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RECENT KNOWLEDGE CONCERNING INFLUENZA *

By RICHARD E. SHOPE, M.D., *Princeton, New Jersey*

FROM the time of Pfeiffer's announcement of its discovery in 1892 [1] to 1918 *H. influenzae* was quite generally regarded as the agent responsible for epidemic influenza. Because of this general belief, much of the huge volume of work done during the 1918–1920 pandemic was concerned with a further study of the relationship of this bacterium to the disease. The results obtained were confused and contradictory; some seemed to support the view that *H. influenzae* was the cause of the pandemic disease, others opposed it. An unbiased review of the large literature on the subject leads to the conclusion that, while the question had still to be considered controversial, the claims for *H. influenzae* as the causative agent of influenza were less convincing after the 1918 pandemic studies than they had been before.

Some of the opponents of the Pfeiffer bacillus theory suspected that the primary etiological agent of influenza might be a filtrable virus. Evidence for the virus theory obtained during the 1918–1920 pandemic was, however, extremely sketchy and unconvincing. A few investigators, notably Selter [2] and Leschke [3] seem to have reproduced the disease in a small number of human subjects by spraying them with filtered respiratory tract secretions and washings from influenza patients. But against these apparently positive results must be placed the negative findings of other workers in much larger series of attempted infections: Kruse,[4] Friedberger and Konitzer,[5] Lister and Taylor,[6] and McCoy, Rosenau et al.[7] entirely failed to produce illness by spraying human subjects with filtered respiratory tract secretions from influenza patients. While it must be admitted that man is a bad experimental animal at best and practically useless when employed for experiment during an epidemic, it is apparent that, so far as published work is concerned, the evidence against a filtrable virus as the cause of influenza was more con-

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From the Department of Animal and Plant Pathology of The Rockefeller Institute for Medical Research, at Princeton, N. J.

vincing than that in favor of it. The conclusion seems warranted that, so far as experimental work done during the 1918–1920 pandemic is applicable, the theory that held influenza to be caused by a filtrable virus was at least as highly controversial as the one which maintained the disease was caused by Pfeiffer's bacillus.

This much of a review of the older work on influenza has been necessary in order to prepare the way for an account of recently acquired knowledge concerning the disease. It is apparent to all, I believe, that one of the most serious handicaps under which earlier investigators worked was the lack of an experimental animal, other than man, susceptible to influenza. It is equally clear now that the recent increase in our knowledge of influenza has resulted largely from the discovery that certain of the experimental animals can be employed in studying the disease.

Swine Influenza

The statement that no animal except man acquires influenza under natural conditions is encountered frequently in the older medical literature. However, in the late summer or early autumn of 1918 a new disease which appeared among swine in the Middle West seemed to challenge this old contention. The new disease was not a sporadic and localized outbreak; actually millions of swine became ill and thousands died during the first few months of its prevalence. By October and November it was widespread among swine herds in Iowa and other parts of the Middle West. Dr. J. S. Koen, who first recognized the disease as being different from any previously encountered in swine, was so much impressed by the coincidental prevalence of human influenza and by the resemblance of the illness seen in man to that occurring at the time in hogs that he became convinced that the two were actually the same.[8] He therefore gave the name "flu" to this new swine disease. The opinion of Koen that "flu" represented an entirely new swine epizoötic disease, and that swine might have been infected in the first instance from man, was shared by some veterinarians and many farmers in the Middle West.[9] Furthermore "flu" proved a generally accepted popular designation for the condition, though in the scientific literature it is usually referred to as "swine influenza." The disease has recurred each autumn, since its first appearance, in epizoötics which vary from year to year in their severity and extent.

Now allowing for certain differences between swine and man, swine and pandemic human influenza were indeed very much alike. In addition to their coincidental prevalence in the autumn of 1918, the clinical and pathological pictures of the two diseases were similar. In both, fever, anorexia, cough and other signs referable to the respiratory tract were prominent, a leukopenia occurred in both diseases, and in both the degree of prostration was out of all proportion to the rest of the clinical picture. In both diseases the onset was sudden, the course short, and convalescence slow but usually uneventful. Both conditions appeared to be highly con-

tagious. Death, when it occurred in either the human or swine disease, was frequently the result of a "water-logged," bloody, edematous pneumonia. It is, of course, evident that all of these similarities could have been a matter of chance and that one is not warranted in drawing conclusions as to the relationship of the two diseases merely on the basis of clinical and pathological resemblances. Their etiological agents should be known and compared. In the beginning, or at the time that swine influenza gained prominence as a veterinary problem, a comparison of this nature was impossible because the causative agent of neither disease was known.

The etiology of swine influenza was finally determined in 1931 and it proved to be different in character from that of any hitherto known disease of animals or man. Instead of being caused by a single agent, swine influenza was found to result from infection with two such agents, one a virus, the other a bacterium, acting synergistically.[10] The virus differed from any previously known, and caused, when administered alone to swine, an extremely mild, indefinite, usually afebrile ailment, which, for want of a better name, was designated "filtrate disease." The bacterium was very similar to, if not identical with, the non-indol producing type of Pfeiffer's *H. influenzae* and was named *H. influenzae suis.*[11] When administered alone to swine it proved non-pathogenic.

Here then in swine influenza was a bacterium like that believed by many to be responsible for influenza in man. Leaving out of consideration for the moment the possibility that *H. influenzae suis* and *H. influenzae* might play analogous rôles in their respective diseases, it was striking to find these similar bacteria closely associated with like diseases occurring in two animal species. The finding furnished additional evidence of a possible relationship between swine and human influenza. Furthermore, the demonstration that swine influenza was caused by the combined activity of this Pfeiffer bacillus-like organism and a filtrable virus made the suggestion obvious that the swine disease might actually be an etiological replica of human influenza. The thing lacking so far as the human disease was concerned, and this was quite important, was positive proof that a filtrable virus was present. Though long suspected, none had been conclusively or convincingly demonstrated. But there was not long to wait.

A Filtrable Virus in Human Influenza

In 1933 Smith, Andrewes, and Laidlaw [12] transmitted a disease to ferrets by inoculating intranasally filtrates of pharyngeal washings from cases of epidemic influenza in man. The ferret disease proved to be serially transmissible, and was characterized by a two-day incubation period, a diphasic temperature response, symptoms of nasal catarrh, and variable systemic disturbances. The mucous membranes of the nasal passages of ferrets killed during the first or second febrile periods were acutely inflamed. In their original work, Smith, Andrewes and Laidlaw recovered the virus from the throat washings of five of eight cases tested and failed to recover it from

four subjects not suffering from influenza. Sera obtained from either recovered ferrets or from patients after an attack of influenza neutralized the virus. All the evidence first presented and that obtained later pointed to the etiological importance of this virus in the disease.

The presence of Smith, Andrewes and Laidlaw's virus in epidemic influenza has been amply confirmed. Francis recovered it from cases of the disease occurring in Puerto Rico,[13] Philadelphia,[14] Alaska,[15] and New York[16]; Burnet isolated it from cases of influenza in Melbourne, Australia[17]; Brightman and Trask found it in an outbreak among children in New Haven[18]; and Smorodintseff and his coworkers demonstrated its presence in an outbreak in Leningrad.[19] Furthermore, Andrewes, Laidlaw and Smith, since their original discovery, have isolated a number of additional strains in England.[20] It is evident that the virus is widely disseminated.

The strains of influenza virus thus far obtained from man have appeared to be identical with one another so far as could be judged by cross-immunity tests and by neutralization tests with sera from recovered animals.[20, 14, 17, 19] However, Magill and Francis, using virus-neutralizing serum prepared in a non-susceptible host, have recently presented evidence that the Puerto Rico and Philadelphia strains differ antigenically.[21] Since these differences were not detectable when sera from recovered susceptible hosts were employed in the cross-neutralization tests, it seems that, for practical immunological purposes, the influenza viruses isolated from patients in various parts of the world must still be considered serologically quite a homogeneous group.

Activities and Properties of Human Influenza Virus

Production of Pneumonia in Ferrets. Francis[13] observed that, after several passages in ferrets anesthetized at the time of inoculation, the Puerto Rico strain of human influenza virus produced pulmonary consolidation in addition to the usual changes it had caused from the beginning in the upper respiratory tract. The pneumonias were of a bloody-edematous character and sometimes proved fatal. Similar passage of the original English strain resulted in its also acquiring the ability to produce pulmonary consolidation.[22]

The Infection of Mice. About a year after the discovery that ferrets were susceptible to influenza virus, Andrewes, Laidlaw and Smith[23] and Francis[13] found that the ferret-adapted virus was also pathogenic for white mice. Administered intranasally to etherized mice, a well-adapted virus caused illness which usually terminated fatally after from three to seven days. At postmortem the only constant changes were in the lungs. These were deep red and almost airless except for small emphysematous areas at the periphery.

Immunity Conferred by Infection. Influenza virus was found to confer immunity upon the animals it infected. Recovered ferrets were not only

solidly immune to reinfection but their sera contained neutralizing antibodies for the virus.[12, 24]

Cultivation and Size of Influenza Virus. The size of the influenza virus particle has been estimated to lie between 80 and 120 mμ on the basis of differential ultrafiltration through collodion membranes [25] and between 87 and 99 mμ as determined by centrifugation.[26]

The virus could not be cultivated upon ordinary bacteriological media although it grew readily in media containing minced chick embryo or upon the chorio-allantoic membrane of the developing hen's egg.[15, 27, 28] It is clear that, like other filtrable viruses, influenza virus requires living cells for its multiplication.

Comparison of the Viruses of Human and Swine Influenza

With the discovery of a virus in human influenza, the fortunes of the swine influenza virus took an unexpected turn. It was found that the virus from swine was also pathogenic for ferrets and mice and that it caused a disease in these two animals which was indistinguishable clinically or pathologically from that produced by ferret-adapted human influenza virus.[12, 23, 29, 30] True, there were certain differences in the initial pathogenicity of the two viruses. Thus, the swine influenza virus when administered intranasally to anesthetized ferrets induced pneumonia even in its first passage whereas the human virus required several serial passages in ferrets before it acquired the ability to cause pulmonary consolidation. In like manner, swine influenza virus proved directly pathogenic for mice while the virus from man was pathogenic for mice only after it had been subjected to several serial transfers in ferrets.* It seems likely that these initial differences in the pathogenic activities of the two agents may be those due to "fixation" by prolonged sojourn in a foreign host since passage of human influenza virus through ferrets alters it in such a way that it becomes more like the swine influenza virus and less like the one originally obtained from man. Human influenza virus, fully adapted to the ferret, produces a disease picture in ferrets and mice that is indistinguishable from that caused in these animals from the outset by swine virus.

While influenza in swine is a disease of complex etiology and both the filtrable virus and *H. influenzae suis* are essential to its causation, the disease in ferrets and mice appeared to be caused solely by the virus. No evidence was obtained to indicate that *H. influenzae suis* or any other bacterium modified the virus infection in these animals in any constant or significant manner.[12, 13, 23, 29, 30]

But the similarity between the swine and human influenza viruses did not end with their like pathogenicity for ferrets and mice. It was found that they immunized against one another. Thus ferrets or mice recovered from infection with swine influenza virus were not only immune to rein-

* Francis and Magill have recently secured strains of influenza virus from man that "took" directly in mice without preliminary ferret passage.[16]

fection with that agent but also usually resisted infection with the human influenza virus. In like manner, animals first infected with human virus were found later to be immune to the swine virus. Such cross-immunity suggested a close immunological relationship between the viruses from man and swine. That the two agents were not actually identical, however, could be shown by cross-neutralization experiments: they could be differentiated serologically.[20, 30, 31] Each virus was completely neutralized by its homologous immune serum though the heterologous immune serum either failed to neutralize or neutralized only partially. The conclusion reached from consideration of cross-immunity and cross-neutralization experiments was that the viruses of human and swine influenza were related but not identical.

The swine influenza virus particle was found to have the same diameter as that of the human virus particle.[25] Swine influenza virus was cultivable in media like that required by the human virus.[21, 27]

The Susceptibility of Swine to Human Influenza Virus

The many similarities between human and swine influenza virus raised the question of whether the human agent might not be pathogenic for swine. This was studied experimentally first by Elkeles [32] and later by Shope and Francis.[33] It was found that swine, inoculated intranasally with human influenza virus alone, developed an extremely mild illness similar clinically and at autopsy to the filtrate disease caused by infection with swine influenza virus alone. When small amounts of a culture of *H. influenzae suis* were administered with the virus a more prostrating febrile illness usually resulted. This was similar to swine influenza although never so severe. At autopsy the pneumonia encountered was of the same character as that seen in swine influenza but much less extensive. The disease caused in swine by the human virus and *H. influenzae suis* could best be characterized as a mild swine influenza similar qualitatively but differing quantitatively from the typical disease occurring naturally in this species.

It was apparent from the work thus far described that the viruses of swine and human influenza were related but not identical. So far as our information went, the human virus, though capable of infecting swine, was probably specific for man; the swine virus was specific for swine.

But this view as to the species specificity of the two agents had to be modified when the influenza virus-neutralizing antibody content of human serum was studied.

Antibodies to Human and Swine Influenza Virus in Human Sera

Smith, Andrewes and Laidlaw [12, 22] had shown that the sera of persons convalescent from influenza neutralized the human virus. Later Francis and Magill,[24] by comparing the antibody content of sera drawn during the acute stage of influenza with that obtained after recovery, demonstrated

that neutralizing antibodies for human influenza virus actually developed during an attack of the disease. From this it seemed likely that their presence in the serum of an individual was an expression of a previous infection with human influenza virus.

Sera from persons of different ages have been studied for their ability to neutralize human and swine influenza virus. The findings obtained in England by Andrewes, Laidlaw and Smith [20] and those gotten in this country by Francis and Magill [34] and Shope [35] were in close agreement. Arranging the cases in three broad age groups it was found, in the English experiments, that the human virus was significantly neutralized by 62 per cent of the sera from persons over 20 years of age, by 57 per cent of the sera from people between 10 and 19 years old and by 33 per cent of the sera from children under 10 years. In the American experiments the human virus was completely neutralized by 48 per cent of the sera from individuals over 20 years of age, by 58 per cent of the sera from people between 10 and 19 years and by 49 per cent of the sera from children under 10 years. It can be seen from these data that, with the exception of the children in the English group, roughly half of the human sera studied neutralized human influenza virus. The incidence of antibodies encountered does not seem surprisingly high in view of the known recent widespread prevalence of the influenza virus.

But the results obtained in the corresponding experiments with swine influenza virus were unexpected. It was found, in the English experiments, that the swine virus was significantly neutralized by the sera from all persons over 20 years of age, by 66 per cent of the sera from individuals between 10 and 19 years but by none of the sera from children under 10 years. In the American experiments the swine virus was completely neutralized by 92 per cent of the sera from persons over 20 years of age, by 63 per cent of the sera from individuals in the 10 to 19 year age group but by only 11 per cent of the sera from children under 10 years. These results were surprising in two respects. First, it was unexpected to find that practically all adult human sera contained antibodies capable of neutralizing a virus that was supposedly specific for swine. Second, since the antibodies were so uniformly present in sera from adults it was surprising indeed to find that they were almost completely lacking in the sera of children. An interpretation of the significance of the findings was difficult because no strain of influenza virus immunologically like the one from swine had ever been recovered from man. The question will be considered more fully later.

Discussion

In considering all of the work thus far done in determining the etiology of influenza in man one is struck by the fact that it can be divided, both chronologically and by subject matter under most intense investigation, into two main periods. During the first period, which extended roughly from the 1889–1890 pandemic through the 1918–1920 pandemic, the interests of

investigators were largely bacteriological and were centered upon the problem of elucidating the rôle played by Pfeiffer's *H. influenzae* in the disease. During the second period, which may be dated from the time of the discovery of a virus in the disease by Smith, Andrewes and Laidlaw up to the present, practically all investigative work has been focused upon the rôle played by this new virus. There has been very little overlapping in the subjects under most intensive study during each of these two periods.

Between the bacteriological and the virus periods of human influenza, investigation into the etiology of swine influenza revealed this disease to be caused by the concerted action of a bacterium like Pfeiffer's bacillus and a filtrable virus. Not only was the swine bacterium like Pfeiffer's bacillus, but experience with it during the first three years' work, in attempting to determine its etiological relationship of swine influenza, closely paralleled the experience investigators of human influenza had had with Pfeiffer's bacillus during the bacteriological period.[11, 36] The arguments for and against considering *H. influenzae suis* etiologically important in swine influenza were much the same as those already debated for many years regarding the causal rôle played by *H. influenzae* in human influenza. Furthermore, the viruses of swine and human influenza were subsequently found to be strikingly alike though not identical. Here then, in the etiology of swine influenza, was what seemed to be a connecting link between the two periods of human influenza investigation: a compromise between Pfeiffer's bacillus on the one hand and a filtrable virus on the other which accepted both as etiologically essential.

But is it justifiable to apply knowledge gained in the study of swine influenza to human influenza? An answer to this question depends partly upon the significance assigned to the swine influenza virus-neutralizing antibodies found in human sera. Two hypotheses to explain the presence of these are apparent. One would interpret them as specific, the other as non-specific, in the sense that, respectively, they had or had not resulted from past infection with swine influenza virus. The non-specific hypothesis will be considered first.

It is known that experimental animals repeatedly exposed to human influenza virus sometimes develop antibodies capable of neutralizing both the human and the swine viruses.[31] Perhaps the swine virus antibodies in human sera were non-specific in the sense that they had been established not by virtue of previous infection with swine influenza virus but rather had resulted from repeated previous exposures to human influenza virus. If this were the correct explanation then all human sera which neutralized the swine virus should also neutralize the human agent. Comparison of duplicate tests against the two types demonstrated clearly that this was not the case: antibodies neutralizing swine virus were frequently present in human sera which failed to neutralize human virus. In these it was evident that the neutralizing antibodies for swine influenza virus had not resulted from previous infection with human virus, unless one chose to believe that the

specific antibodies for the human virus disappeared after each influenzal infection while the non-specific swine virus antibodies persisted and were gradually built up by each succeeding attack of influenza. There are as yet no data to indicate that this conjecture is likely or even possible.

The hypothesis which interprets the swine virus-neutralizing antibodies in human sera as specific and to have resulted from past infection with a virus whose antigenic composition was similar to that of swine influenza, just as the human virus antibodies are considered to reflect a past infection with human influenza virus, is more in harmony with the facts determined by animal experimentation. On the basis of this interpretation it is apparent that human sera contain neutralizing antibodies for at least two immunologically distinct types of influenza virus. One is the current human virus of Smith, Andrewes and Laidlaw known to be widely prevalent in man at the present time. The other, antigenically like swine influenza virus, is unknown and has never been detected in man. It has, however, left ample evidence of its past widespread prevalence in the form of neutralizing antibodies in the sera of almost all adult human beings. That it is no longer widely existent in the human population is indicated not only by the failure of investigators to recover it from cases of influenza during the past four years, but by the almost complete absence of antibodies for it in the sera of children. If one ascribes a specific character to the swine virus-neutralizing antibodies in human sera, the conclusion that this unknown human virus was indeed swine influenza virus, or a closely related agent, is inescapable.

However, there is no direct evidence that the swine influenza virus, as we know it today, is capable of infecting man. Indeed, indirect evidence indicates that it does not infect man because, while swine influenza has occurred annually since 1918, our serological evidence suggests that the human prototype of swine influenza virus ceased infecting man generally 10 or more years ago.

The most apparent interpretation of these findings is that the swine virus represents a surviving form of an extinct or temporarily quiescent human influenza virus which has become so "fixed" in swine as to be no longer pathogenic for human beings. If this is the case, then the history that swine influenza appeared for the first time in 1918 serves to date the time of prevalence of this vanished human virus. The experimental and historical facts seem best explained, for the present at least, by the theory that the swine influenza virus represents a surviving form of that pandemic in man in 1918, as already suggested by Laidlaw.[37] On this basis, the presence in human sera of antibodies neutralizing swine virus would be considered to indicate that the donors of these sera had undergone immunizing exposures to, or infections with, an influenza virus of the 1918 pandemic type. Thus it seems possible that swine influenza may represent more than merely an interesting analogue of the human disease, it may actually bear a relationship to pandemic influenza.

The matter of determining the relationship between the influenzas of swine and man is of importance only in so far as it bears upon the question of the etiology of the human disease. The causative agents of the swine disease are known. Furthermore, agents of a similar nature are present in the human disease. Do these agents play the same rôle in pandemic human influenza that they are known to play in swine influenza? I have purposely, in this paper, called attention to the close similarity that exists between the disease pictures of influenza in swine and pandemic influenza in man; to the suggestive history that swine influenza made its first known appearance during a great human pandemic; to the apparent identity of the predominant bacterium in the human disease with the one known to be etiologically essential in the swine disease; to the close relationship between the viruses of human and swine influenza; and to the presence in human sera of neutralizing antibodies for both the human and swine viruses. Any one of the parallelisms might be fortuitous; it seems unlikely that all should be.

The possibility must, of course, be kept in mind that human beings may resemble ferrets and mice more closely than they do swine in their reaction to influenza virus. In this event the virus would be considered the sole and primary etiological agent of influenza and any associated bacteria would be thought of as merely concomitant and of secondary importance. However, the disease caused in ferrets and mice by the human influenza virus alone may be just as highly artificial in reflecting the complete etiology of human influenza as is that caused in the same animals by swine influenza virus alone in reflecting the complete etiology of the swine disease. It remains to be determined whether pandemic influenza in man is a disease like that in ferrets and mice caused by infection with the virus alone or whether it resembles swine influenza and requires both the virus and a bacterium. Personally, I am of the opinion that the virus of human influenza, like that of swine influenza, constitutes only a partial etiology of the disease in which it is involved and that workers of the bacteriological period who contended for the etiological importance of Pfeiffer's bacillus may have been at least partially right.

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CLINICAL INVESTIGATIONS OF INSULINS WITH PROLONGED ACTIVITY *

By Russell M. Wilder, Ph.D., M.D., F.A.C.P., *Rochester, Minnesota*

A year ago, at the meeting of the American College of Physicians, Dr. Joslin expressed the opinion that Hagedorn by effectively retarding the action of insulin with protamines had opened a new era in the treatment of diabetes. During the past year hundreds of physicians have had the opportunity to use protamine insulin in the treatment of diabetes, and I am informed that their verdict is almost unanimously favorable. In February of this year an improved modification of Hagedorn's preparation was placed on the market. It already had received the official endorsement of the Insulin Committee in Toronto and that of the Council on Pharmacy and Chemistry of the American Medical Association.

I propose in this paper to recount certain clinical investigations which illustrate some of the peculiarities of the action of insulins with retarded activity, and in part explain the advantages attending their use.

A pitfall to be avoided when studying the effect in diabetes of drugs and diets, is the trial of the remedy in cases in which the diabetes is of short duration. This mistake in the past has led to a number of erroneous conceptions; the notions, for instance, that dark breads can be tolerated better than white breads and that honey and maple sugar are less harmful than other sweets. Quackery in diabetes thrives because of the tendency for spontaneous remission in the early course of this disease. Tolerance for carbohydrate improves during the first year or two, if only minor attention is paid to limiting the intake of carbohydrate, and the credit is given, undeservedly, to the medicine used or the special food. The patients who kindly consented to serve as subjects for these clinical investigations had had diabetes for five years or longer.

Mild diabetes also can mislead the observer, by fluctuating in intensity. Furthermore, arteriosclerosis and certain other complications of diabetes sometimes decrease the sensitivity of the patient to overdoses of insulin, and under these circumstances enough unmodified insulin may be administered in one injection to prevent hyperglycemia for 24 hours. Because of this fact we chose patients who were hypersensitive to overdoses of insulin; they previously had been more or less refractory to satisfactory control, and most of them were "pedigreed," in the sense in which Dr. Woodyatt has used this term; that is, they had been studied before, some of them many times, so that the characteristics of their disease were known.

* The Trimble Lecture, Medical and Chirurgical Faculty of the State of Maryland, Baltimore, Maryland, April 28, 1937; also presented in part to the American College of Physicians, St. Louis, Missouri, April 19, 1937, under the title "Protamine and Other Long-Acting Insulins."

The work to be presented represents the combined efforts of several of us. My associates include Drs. Edwin J. Kepler, Edward H. Rynearson and Jesse Bollman, and the following Fellows of The Mayo Foundation for Medical Education and Research: Randall C. Sprague, Benjamin B. Blum, Bertha M. Davis Clark, Reid R. Heffner, Clarence W. Erickson, James A. Barr, Donald W. Ingham and George R. Crisler. For the necessarily arduous analytical work we are indebted to Dr. Arnold E. Osterberg and members of his department, and for much assistance our thanks are due to Miss Mary A. Foley, Sister Mary Victor, Sister Rebecca and others in the dietetic and nursing departments of the St. Mary's and Kahler hospitals. The preparation of protamine insulin came from the Eli Lilly Company of Indianapolis; the crystalline insulin was supplied by Stearns and Company of Detroit.

The Prolonged Action of Protamine Insulin

Our first observation revealed that the claim for prolongation of action of protamine insulin was fully warranted (figure 1). A woman, aged 49

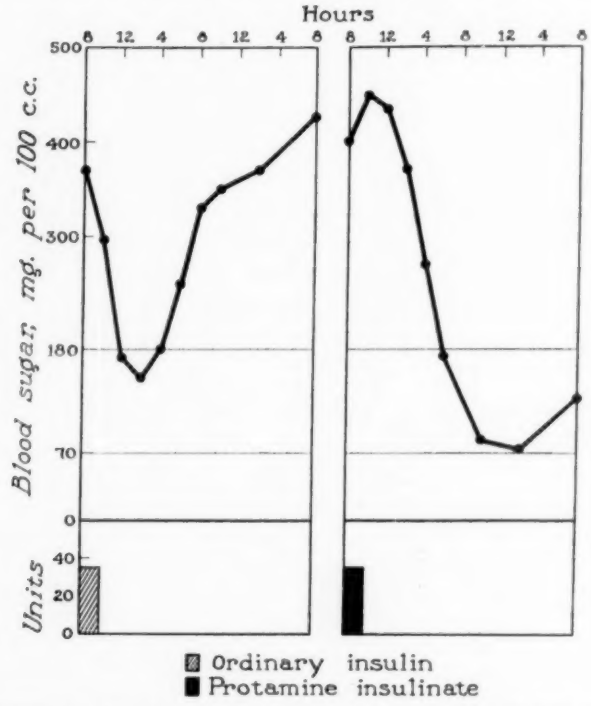

Fig. 1. Comparative duration of action of ordinary insulin and protamine insulin.

years, who had had severe diabetes for nine years, was given 35 units of unmodified insulin 20 minutes before breakfast. The breakfast contained 30 gm. of carbohydrate, 18 gm. of protein, and 44 gm. of fat. The level of the blood sugar fell from its fasting value of 370 mg. per 100 c.c. and

reached a minimum of 150 mg. per 100 c.c. in six hours. The noon and evening meals were withheld, and no more insulin was used. The value for the blood sugar rose as rapidly as it had fallen. By the following morning it stood at 425 mg. per 100 c.c. and the value for the carbon dioxide combining power of the plasma was 28 volumes per cent. One cannot say with certainty at just what hour, in this observation, the action of the insulin terminated, because a blood sugar time curve is an expression of several variables. However, it is reasonable to regard the point at which the curve rose above the renal threshold for dextrose (about 180 mg.) as marking the end of the action of insulin. By this arbitrary standard, the 35 unit dose, in this case, acted for eight hours.

On another day, with conditions as nearly identical as possible, an equal dose of plain protamine insulin was followed by an increase in the value for the blood sugar after breakfast from 400 to 449 mg. per 100 c.c. Then a prolonged fall occurred. The low point, 72 mg. per 100 c.c., was reached 18 hours after the injection, and the next morning there still was evidence of the activity of insulin. The value for the blood sugar then was only 148 mg. per 100 c.c., and glycosuria and evidence of acidosis were absent.

This observation, and others to be described, led us to anticipate that protamine insulin might be given in one dose each 24 hours. Especially should this be possible if the injection was made in the morning, so that the peak effect would come at the proper time to be buffered by the hyperglycemic effect of food eaten during the day. We put this plan of treatment to trial, and soon were convinced of its desirability. The same plan has been adopted in Toronto and elsewhere. The convenience to the patient of being able to take in the morning all the insulin he needs for the day is not inconsiderable. In milder cases protamine insulin alone has been used; in more severe cases a supplementary dose of an insulin with prompter action has been necessary.

Comparative Action of Plain, Calcium, and Zinc Protamine Insulins

Soon after the introduction of protamine insulin it became apparent that the stability of the precipitate would have to be increased before it could be made available commercially. Suspensions of the original preparation, after standing for several days, would lose some of their potency, due to adherence of the precipitate to the sides of the bottle. The manufacturers overcame the difficulty by adding small amounts of soluble salts of calcium (1 or 2 mg. of calcium per 100 units) or of zinc (1 mg. of zinc per 500 units). The additions, it was found, also changed the duration of action of the insulin. Calcium shortened the period of action, while zinc had the opposite effect. Zinc also formed a more stable precipitate. It is for these reasons it now is regularly incorporated in the preparation which has been placed on the market.

The relative intensity and duration of action of protamine insulin with and without additions of calcium or zinc are illustrated (figure 2). The subject of these observations was a girl, aged sixteen years, who had been diabetic for 10 years and required about 80 units of unmodified insulin daily. In each observation 50 units of the preparation to be studied were injected, and food was withheld for the next 48 hours. Between each study the patient was treated for several days with unmodified insulin, the last dose being given 14 hours before the start of the next injection of a protamine preparation. Thus, a high value for the fasting blood sugar was insured, and the durations of action of the various preparations could be compared under similar conditions. At the forty-eighth hour after the administration of

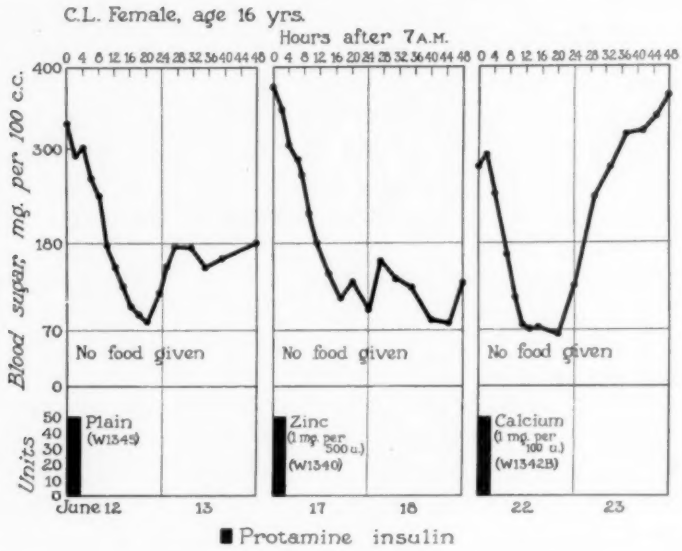

FIG. 2. Comparative duration of action of plain, calcium, and zinc protamine insulins.

50 units of plain protamine insulin, activity was almost spent; the blood sugar curve had risen to the renal threshold. At the forty-eighth hour after the administration of an equal dose of protamine insulin containing 1 mg. of zinc per 500 units, the value for the blood sugar was still near its minimal point, which was evidence of continued strong action of insulin. When 50 units of the preparation containing 1 mg. of calcium per 100 units were given, the value for the blood sugar passed the renal threshold by the twenty-eighth hour.

STUDIES OF PROLONGED HYPOGLYCEMIA

Many a diabetic, using unmodified insulin, has had insulin reactions in his sleep, with only a headache or sore muscles or a bitten tongue the following morning to inform him of the episode. The spontaneous recovery is

attributable to the fact that the action of unmodified insulin is spent in a relatively few hours and hepatic glycogenolysis begins as soon as the insulin is exhausted. The prolonged action of protamine insulin made it seem possible that a resulting hypoglycemia might not be recovered from spontaneously, and we became apprehensive for patients who, using protamine insulin, might fail to get their food. An attack of migraine, for instance, might interfere with the retention of food and have serious consequences. Therefore, the duration and severity of the hypoglycemia produced by protamine insulin in patients who fasted were made the subject of investigation.

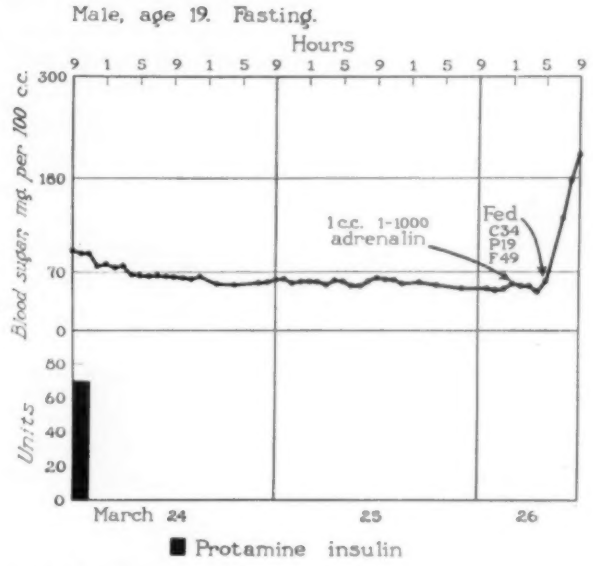

FIG. 3. Prolonged hypoglycemia from administration of protamine insulin to a fasting diabetic subject.

In one study (figure 3) a young man, who had been a diabetic for six years, received 70 units of plain protamine insulin. This dose previously had been given every morning and was what was required to prevent glycosuria. The value for the blood sugar at the time was 94 mg. per 100 c.c. It fell gradually to a low level of 45 mg. and remained between 45 and 62 mg. for the last 38 hours of a fast of 57 hours. There were no notable symptoms until late. In the fifty-second hour the patient became restless and irrational, the tendon reflexes were exaggerated, the pupils were dilated, and the value for the systolic blood pressure rose to 150 mm. of mercury from previous readings of about 120 mm. The condition of the patient was much improved 10 minutes later by the injection of 1 c.c. of a 1:1000 solution of epinephrine, although the values for the blood sugar, determined at intervals of 15 minutes after administering the epinephrine, had not changed significantly. The fast was terminated in the fifty-seventh hour because of the reappearance of symptoms.

This observation, and others like it, showed that when hypoglycemia is produced very gradually it may not be attended by the stormy symptoms characteristic of the reactions to unmodified insulin. Subsequent experience has confirmed this conclusion. If a patient rests in bed, after overdoses of protamine insulin, symptoms may be absent entirely or appear very late. If he is up and about they are more likely to be manifest because exercise provokes them. As a rule, however, they differ from those with which patients and physicians, using unmodified insulin, have become familiar. The phenomena which probably have been attributed correctly to a protective mobilization of epinephrine are less pronounced. The value for the blood sugar falls so gradually that the suprarenal glands are not aroused. Therefore, tremor, sweating, tachycardia and pounding pulses usually are missing, and their place is taken by symptoms of cerebral origin, such as lassitude, fatigue, headache or nausea.

It appeared from studies like the one I have cited (figure 3) that loss of consciousness was less likely to occur after the use of protamine insulin, and that hypoglycemia could be tolerated for many hours without serious consequences. This was reassuring. However, symptoms of cerebral irritation were apparent before the termination of the fast, and we have found (Bollman) that dogs made hypoglycemic for several days with protamine insulin would die of convulsions when dextrose was given to restore them. Multiple petechial hemorrhages were scattered throughout the brains of these animals. Therefore, it was not to be concluded that long-continued hypoglycemia was harmless, and we were led to recommend that patients take sugar at intervals of half an hour if meals were missed or whenever unusual symptoms suggested overdosage. Experience later revealed that hypoglycemia may return after treatment or even after meals, and therefore the patients were advised that the doses of sugar administered at intervals of half an hour were to be resumed if the symptoms returned.

The Effect of the Type of Diet on the Control of Glycosuria

There has been much difference of opinion as to what type of diet gives the best results in the practical management of diabetes. Many physicians have followed the recent trend toward allowing relatively large amounts of carbohydrate. Others have adhered to the principles established by Naunyn, and are keeping the intake of carbohydrate low. Others have taken the middle road, planning diets with greater reference to general nutritional considerations.

Two young men, aged 18 and 20 years respectively, who had diabetes of maximal severity, were given first low and later high carbohydrate diets and single morning injections of protamine insulin (figure 4). In each case the loss of dextrose in the urine was considerably greater after administration of the high carbohydrate diet than it was after administration of the low carbohydrate diet, as was the average of the five blood

sugar determinations made each day. The average level of the morning blood sugar, on the other hand, was lower during the days on which the high carbohydrate diets were administered. These postabsorptive levels were so low, indeed, that it was impossible without provoking reactions to use larger doses of protamine insulin in an attempt to control the daytime hyperglycemia and glycosuria. This and other experience has dissuaded us from resorting to diets containing more than about 150 gm. of carbohydrate when patients are treated with protamine insulin. Some patients,

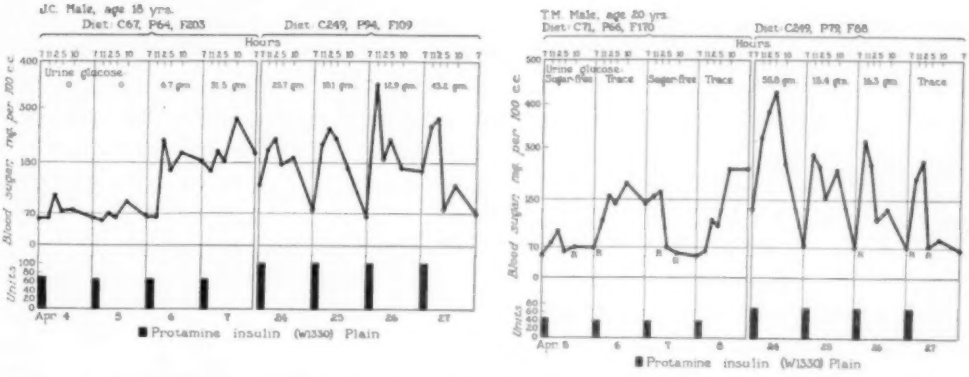

FIG. 4. Comparative effect of low and high carbohydrate diets in patients treated with protamine insulin.

however, do well with more liberal amounts, as is illustrated by the following observation (figure 5).

A diabetic woman, aged 47 years, who required 50 units of protamine insulin on a measured diet containing 140 gm. of carbohydrate, was given 60 units a day and served food from the general kitchen. Only candy and table sugar were withheld. On the first day of the general diet, 14.2 gm. of sugar were excreted in the urine, but on the days that followed there was never more than a trace of sugar. This patient probably represented the type of adult diabetic whose blood sugar is not easily depressed below normal levels by unnecessarily large amounts of insulin. On the basis of the result, it would appear that in cases of the insulin-insensitive type of diabetes greater latitude in the amounts and quality of food may be permissible with the use of protamine insulin. Subsequent experience has confirmed this conclusion, although this type of treatment is not recommended.

OBSERVATIONS OF THE ACTION OF CRYSTALLINE INSULIN

About a year ago announcement was made of prolonged hypoglycemic action obtained with solutions of crystalline insulin. Since then, other reports have led to the assumption that the action of this crystalline insulin is comparable to that of protamine insulin. Our experience is different. We have been supplied with the material through the courtesy of the in-

ventor of a commercial method for its production, and our studies show that while its action is longer than that of unmodified insulin it is not long enough to permit treatment of severe diabetes with fewer injections than two a day. The preparation cannot take the place of protamine insulin; on the other hand, either this preparation, or one with a similarly intermediate duration of action, would be useful as an adjunct in the treatment of certain diabetic patients.

I already have stated that when diabetes is severe, sugar often appears after meals unless supplementary, quick-acting insulin is given with the morning dose of protamine insulin. The degree of glycosuria observed under these circumstances may be harmless, but until we have proof of its harmlessness we must insist on its control. This means using supplementary insulin, and for this purpose an insulin with action like that of

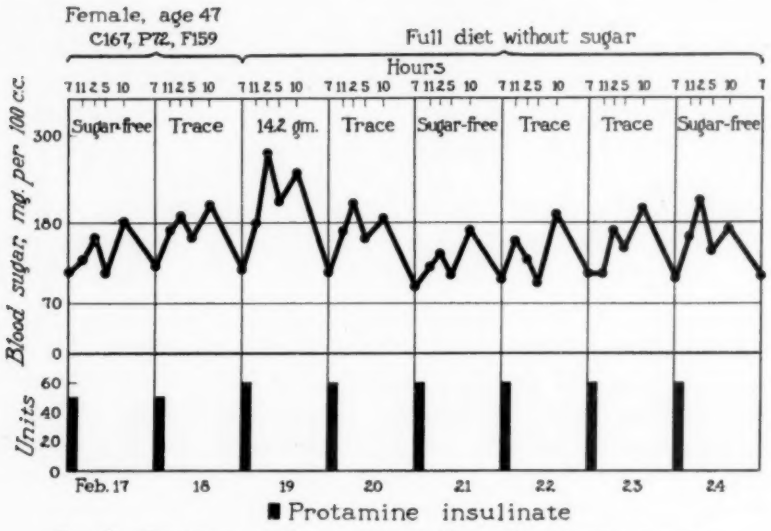

FIG. 5. Treatment with unrestricted diet and protamine insulin.

crystalline insulin would be very useful. Ordinary unmodified insulin is not satisfactory because its action is spent too early. The preparation of crystalline insulin that we have studied represents exactly what is needed. Its action is long enough so that when it is injected in the morning, together with the dose of protamine insulin, it amplifies the hypoglycemic effect during the day and prevents glycosuria after meals. By evening, however, its action has been spent, and thus the hypoglycemic effect of the protamine insulin is not exaggerated during the night.

An ideal insulin would be one which combined the activity of the right dose of protamine insulin with that of the right dose either of crystalline insulin or a preparation of similar behavior. Unfortunately, a good many difficulties stand in the way of achieving this. One patient would require more of the quick and less of the slow action, while another would need

more of the slow and less of the quick action. Such an insulin, therefore, would have to be "tailor-made" for the individual, as Dr. Campbell has suggested. A more likely solution of the difficulty may be expected from the preparation of a protamine insulin to which a quick-acting insulin can be added as required. At present, protamine insulin contains an excess of protamine, and thereby unmodified insulin which is added to it is precipitated. Possibly a way can be found to overcome the necessity for this excess. Until then, if supplementary doses of quick-acting insulin are to be given, the patient must take these separately, using a clean syringe for each injection.

I am showing data bearing on the duration of action of preparations of crystalline insulin, partly because of the interest in this subject and also because these data provide other information of practical significance in the treatment of diabetes.

An experiment I have described (figure 1), in which a single dose of insulin was given in the morning followed by breakfast but no other meals, was repeated several times to determine the relative duration of action of crystalline and protamine insulin. The volunteer diabetic patient who served in the first study of this type also consented to serve as the subject of these later studies. Before each observation she was maintained with unmodified insulin for a period of three days to avoid any holdover effects from previous injections of protamine insulin. In each observation the dose of insulin was the same, 35 units, and the breakfast always consisted of 30 gm. of carbohydrate, 19 gm. of protein and 44 gm. of fat. It represented the breakfast of her maintenance diet.

In the observation of January 11 to 12, the insulin used was a solution of a special crystalline insulin. The blood sugar time curve is shown in figure 6. The data reveal that the insulin was spent before the twentieth hour. By the twenty-fourth hour signs of impending acidosis were present. In the observation of January 15 to 16 (figure 6) protamine zinc insulin was used in the same dosage (35 units). This produced an equal degree of hypoglycemia, more tardily, but maintained the blood sugar at a low level until after the twenty-eighth hour. Also, no sugar appeared in the urine until the fortieth hour, and there were no signs of acidosis until the forty-fourth hour.

These data illustrate what I have said, namely, that the action of the crystalline preparation is retarded considerably more than is that of unmodified insulin, but that the retardation of crystalline insulin is not comparable to that of protamine insulin.

Protein Wastage Prevented with Protamine Insulin

In an observation made January 22 to 23, the patient who had been the subject of the observations of January 11 to 12 and January 15 to 16 was given 35 units of the preparation of crystalline insulin used before. In-

stead of a breakfast, however, followed by prolonged fasting, she received food every two hours. The feeding consisted of a mixture of milk and cream, so arranged that each feeding would supply amounts of carbohydrate, protein and fat comparable to a twelfth of the amounts of these food factors in the maintenance diet. The data are recorded in figure 7. It was observed that the duration of hypoglycemia did not exceed 12 hours, that sugar appeared in the urine by then, and that after 16 hours the excretion of nitrogen was greatly increased.

The observation made on January 22 to 23 was repeated February 5 to 6, with a preparation of crystalline insulin to which zinc had been added (figure 8). The course of events was almost the same as it had been before, although the action of the insulin was intensified slightly and con-

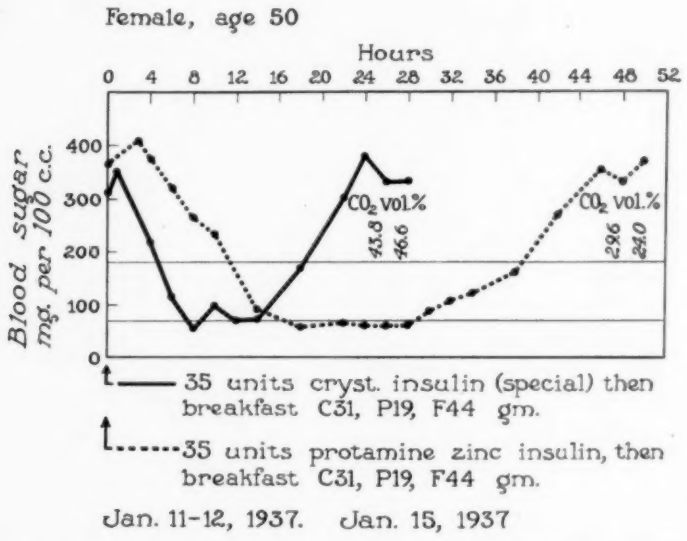

FIG. 6. Comparative duration of action of a special crystalline insulin and protamine zinc insulin.

tinued about four hours longer. Even so, evidence of insulin activity had passed by the sixteenth hour. The value for the blood sugar was increased, the urine contained sugar and the excretion of nitrogen was increased.

Attention is invited to the behavior of the metabolic balance for nitrogen in these studies. The inflow of the nutriment at a continuous rate, accomplished by feeding the mixture of milk and cream at two-hour intervals, and the collection of urine at intervals of exactly four hours, made it possible to obtain this balance for a succession of four-hour periods. The patient at the beginning of each study had been given no insulin for 14 hours, and that insulin was unmodified insulin. No long-acting insulin had been used for several days, and since the case was one of severe diabetes, insulin action at the beginning of each study probably was minimal.

The negative balance for nitrogen of the first four-hour period in both studies is accounted for, I believe, by this circumstance. The sparing effect on protein of insulin given at the beginning of each study was not evident until after the first period. This delay is readily explained by the time necessary for absorption of the insulin. The effect of this insulin shows itself in the diminished excretion of nitrogen in the second, third and fourth periods. As the observations proceeded, a time was reached in each study when the excretion of nitrogen again rose and a negative

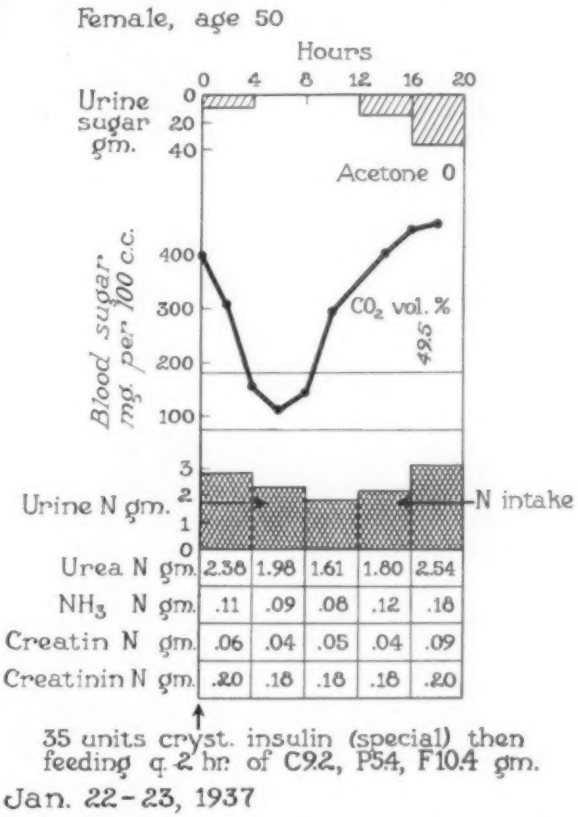

FIG. 7. Negative nitrogen balance before and after period of activity of a dose of crystalline insulin.

balance again was observed. This time coincided roughly, in each case, with the time when the blood sugar curve rose above the renal threshold for dextrose.

The behavior of the balance for nitrogen in these studies would have escaped detection except for collection of the urines in four-hour periods, and the analysis of these separately for their content of nitrogen. Examinations of 24 hour collections would not have indicated negative balances for nitrogen, for the reason that the loss of nitrogen during the periods when

insulin was inactive would have been offset by the retention of nitrogen in the other periods.

Negative balances for nitrogen have long been observed in cases in which severe diabetes is out of control; the condition formerly was called "azoturia," but so far as I know, it has not been demonstrated before that azoturia occurs so soon after the period of activity of a preceding dose of insulin. The phenomenon is not without practical importance. Patients treated with unmodified insulin are commonly given one dose before each

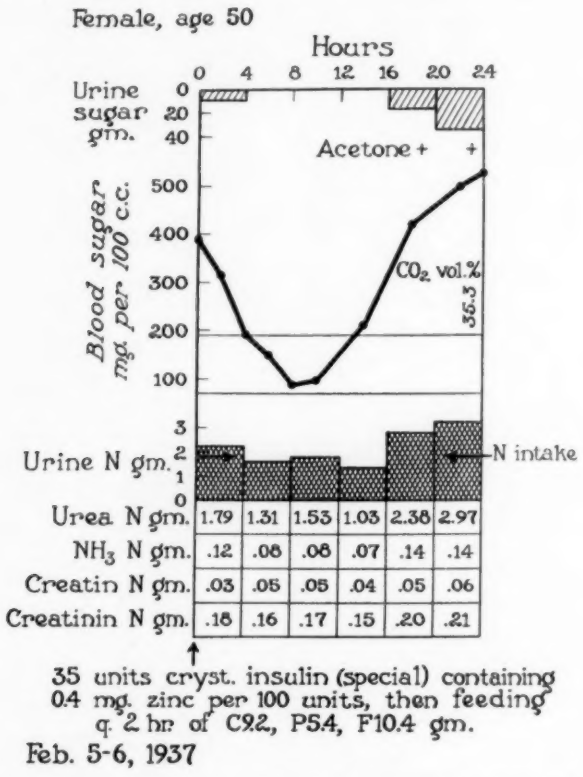

FIG. 8. A longer period of activity was imparted to crystalline insulin by the addition of zinc; negative nitrogen balances occurred before and after period of insulin activity.

meal, or two doses, one before breakfast, the other before supper. The time of action of unmodified insulin is not more than eight hours, and under these circumstances the balance for nitrogen may become negative for one or more short periods in each 24 hours. In these periods the protein of the body is subjected to drainage of its amino-acids to supply material out of which the liver can manufacture sugar. Intracellular as well as deposit-protein may be drawn upon, to judge from the increased excretion of creatine and creatinine which was observed when the balance for nitrogen was negative in the studies mentioned (figures 7 and 8).

It has been a common observation of those who have had experience with protamine insulin that patients receiving preparations of it gain in strength and fitness. Improvement has been noticeable, particularly in individuals who previously, using unmodified insulin, were not perfectly controlled. It is not always possible with protamine insulin to obtain complete control in cases of severe diabetes, but even when the control with protamine insulin is imperfect the patients say they feel better, and gradual improvement in tolerance for carbohydrate may be observed. I suggest that the reason for the improved sense of well-being of such patients and the improvement in their tolerance may be attributable to the avoidance of intermittent periods of azoturia.

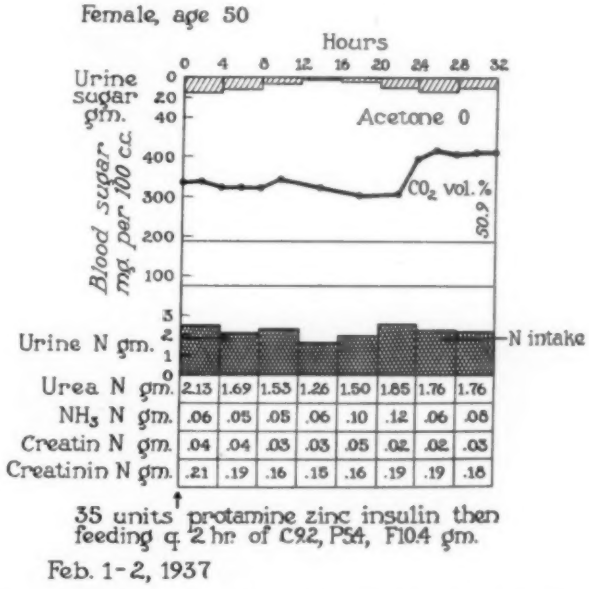

FIG. 9. A dose of protamine zinc insulin, which was too small to control glycosuria, prevented significant loss of nitrogen for 32 hours.

This hypothesis is supported by the following evidence. In an observation made February 1 to 2 (figure 9), planned exactly like those of January 22 to 23 and February 5 to 6, protamine zinc insulin was given. The same patient submitted to the observation and the number of units of insulin which were administered was the same. Again, a negative nitrogen balance was observed in the first four-hour period. The amount of protamine insulin was not enough to lower the blood sugar below the level at which it was found in the morning. It, therefore, was inadequate to suppress glycosuria and yet the excretion of nitrogen was depressed after the first four hours; it remained below the level of the intake of nitrogen until the end of the twentieth hour. The balance was still not grossly negative even after 31 hours.

Similar data were obtained in another study. The patient in this case was a young woman who had diabetes of extreme severity. It antedated the introduction of Banting's insulin. Protamine insulin containing calcium was given in two observations (figure 10 and 11), and zinc protamine insulin was given in a third (figure 12). A protein sparing effect was evidenced each time by diminished excretion of nitrogen after the first period. With the preparations containing calcium the sparing effect lasted for only 24 hours, but with the preparation containing zinc it was still apparent in the period between the thirty-second and thirty-sixth hours. In this last

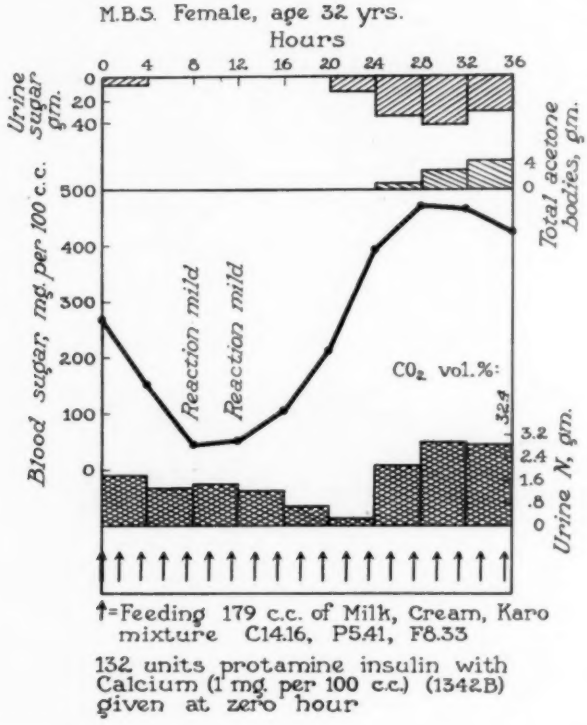

FIG. 10. An injection of protamine insulin with added calcium inhibited excretion of nitrogen for 24 hours; the period of activity was followed by azoturia.

period the value for the blood sugar stood at almost as high a level as it had in the beginning of the experiment, and 16 gm. of sugar were excreted in the urine.

The results of these observations also bear on the question I raised before, whether glycosuria after meals is harmful when patients are treated with protamine insulin. They show that moderate glycosuria under these circumstances is not attended with azoturia, which may mean that such glycosuria is not as harmful as that which occurs in intervals between the periods of activity of doses of unmodified insulin. The prevention of pe-

riods of azoturia by the use of protamine insulin may even mean that those degenerative disorders which so frequently complicate diabetes—retinitis, neuritis, and arteriosclerosis—will occur less frequently, or if present, will develop less rapidly, but more time must pass before this can be determined.

Protamine Insulin in the Treatment of Diabetic Acidosis

A final topic demanding brief mention is the use of protamine insulin in the treatment of diabetic acidosis. It was the general belief a year ago

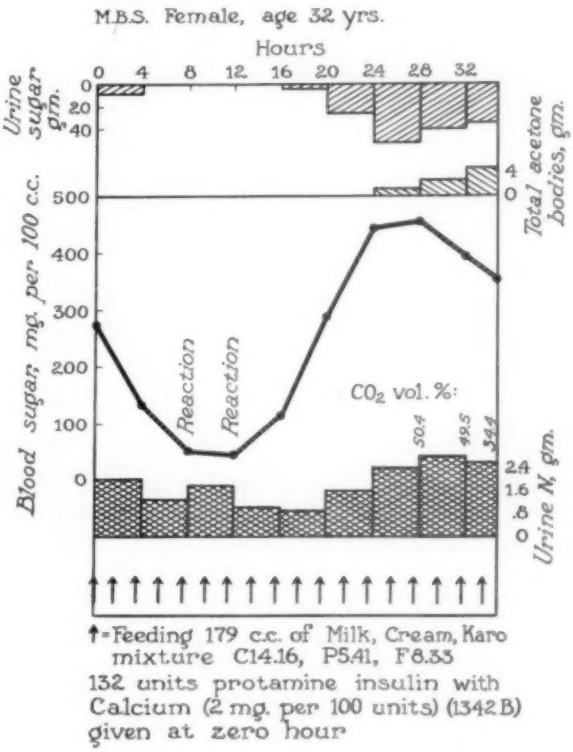

Fig. 11. An injection of protamine with added calcium inhibited excretion of nitrogen for 24 hours.

that the retarded action of the new insulin made it undesirable for use in emergencies. My associates and I now are convinced that this opinion is mistaken, and that a dose of protamine zinc insulin used together with quick-acting insulin, is of advantage. A report of some of our experiences with this has already been made by Kepler, Ingham and Crisler. The slow absorption of protamine insulin guarantees a continuous supply of insulin to the circulation. Thus, continuous action is effected no matter how rapidly insulin may be exhausted after it enters the circulation. A continuous insulin effect is difficult to obtain in acidosis by injecting unmodified insulin

at intervals such as usually are chosen, for the reason probably that insulin after its absorption is destroyed more rapidly than usual. Our practice now is to give protamine insulin at the beginning of treatment, in a dose of from 50 to 100 units, and thereafter to treat the patient in the conventional manner with the multiple doses of unmodified insulin that are suggested by frequent tests of the blood and urine. We have treated seven patients who had diabetic acidosis, in this way, and the results have been surprisingly satisfactory. The doses of unmodified insulin found necessary in all but one case have been much smaller than expected, the time required to restore

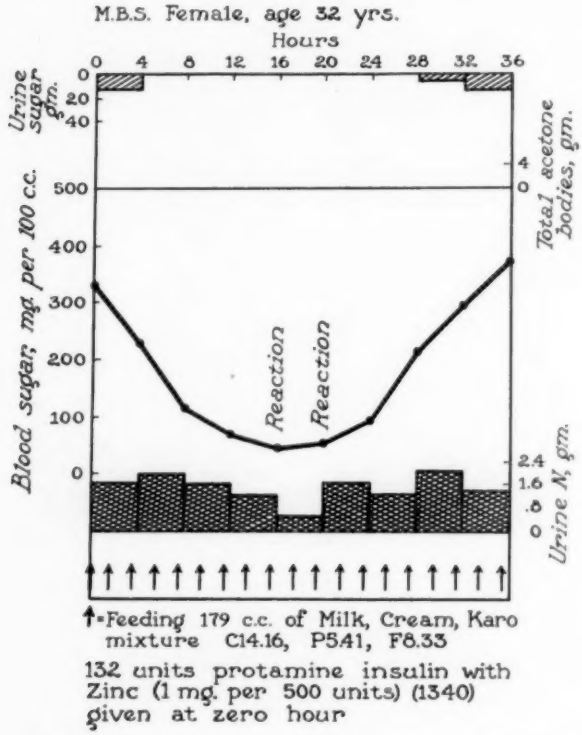

FIG. 12. An injection of zinc protamine insulin inhibited loss of nitrogen for 36 hours, despite the hyperglycemia and glycosuria which occurred after the twenty-eighth hour.

the patient has been shortened, and the period of continued insensitivity to insulin, which usually is encountered after attacks of acidosis, has been avoided. Possibly we have had a series of unusually favorable cases, but I am quite sure this is not the entire explanation. The patients in two instances were in profound coma.

The data in the last case of acidosis, at this writing, are shown (table 1). The patient was 59 years of age. The recent statistical data on diabetic acidosis reported from the clinic by Dr. Baker and from the Deaconess Hospital by Dr. Joslin and his associates, show a mortality of about 40 per

TABLE I

Treatment of Diabetic Acidosis

	March 17, 1937					March 18, 1937				March 19, 1937				March 20, 1937			
	a.m.		p.m.			a.m.		p.m.		a.m.		p.m.		a.m.		p.m.	
	9:30	11:00*	2	5	10†	8	11‡	4	10	7	11	4	10	7	11	4	10
Blood:																	
Sugar, mg. per 100 c.c.	594	540	306	136	54	297											
CO_2 combining power, volumes per cent	17.4	13.5	31.5	46.6	57	57											
Urine:																	
Sugar, grade	4			4			4	3	4	2	0	1	0	0	0	0	0
Acetone, grade	3			3			0	0	0	0	0	0	0	0	0	0	0
Insulin, units:																	
Protamine	100						40			40				30			
Unmodified	50	30	10				10			10							

* Urea 72, sodium 299, potassium 20.4, calcium 10.6, chlorides 300, sulphates 5.8, phosphorus 6.0 mg. and protein 8.8 gm., per 100 c.c. of blood plasma or serum. Began administration of: 0.9 per cent sodium chloride (2000 c.c. given in 3 hours). Sodium bicarbonate, 5 per cent, intravenously (300 c.c. given in 1 hour.) (300 c.c. of the solution of sodium bicarbonate left in stomach after lavage).

† Began administration of orange juice at 2-hour intervals. (650 c.c. given in 10 hours.)

‡ Diet started: Carbohydrate 140, protein 59, and fat 119 gm.

cent for patients in the sixth decade who require treatment for acidosis. Diabetes had been present for five years and the dose of insulin had been 40 units daily (two injections daily, each of 20 units of unmodified insulin). The attack was precipitated by the failure of the patient to take insulin. I am thankful to say that she was not a graduate of our diabetic school. She accompanied a relative and was not intending to consult us about herself. She became fatigued on a Sunday, by a long automobile journey, was disinclined to eat supper and omitted the dose of insulin. She was nauseated on Monday, and omitted meals and insulin. She took 20 units of unmodified insulin on Tuesday morning, but none that evening. She began to vomit during the night, and on Wednesday morning called a physician. She was drowsy on admission to the hospital, but not unresponsive. Her breath smelled strongly of acetone and the respiration was markedly hyperpneic. The skin and tongue were dry. Extreme thirst and abdominal pain were the chief complaints. The balance of the story is told by the data in the table. Suffice it to add that this patient was so well by the fifth day that no amount of insistence could dissuade her from leaving the hospital.

SUMMARY

Selected observations have been presented to illustrate some of the peculiarities of the action of preparations of protamine and crystalline insulins. Conclusions based on these and other studies are as follows:

The activity of protamine insulin is prolonged for more than 48 hours

in fasting diabetic patients. The period of activity of unmodified insulin is less than 12 hours in fasting patients.

Further prolongation of action has been effected by the amount of zinc contained in the preparation of protamine insulin recently placed on the market. The addition of calcium shortens the duration of activity.

Symptoms may be absent for many hours in fasting patients who are made severely hypoglycemic by the administration of protamine insulin. When symptoms finally appear they are likely to be limited to those of cerebral origin, such as lassitude, fatigue, headache, and nausea.

Greater instability of the level of the blood sugar adds to the difficulties of treatment with protamine insulin, when much carbohydrate is included in the diet. This may not be true in cases of the type of diabetes characterized by insensitivity to overdoses of insulin.

The duration of action of solutions of previously crystallized insulin is intermediate. It does not extend beyond 12 or 14 hours when patients receive food. The duration of action of protamine insulin when food was given exceeded 36 hours.

The experimental data presented illustrate the importance of insulin in protecting the proteins of the body from catalysis. They reveal, furthermore, that in severe cases of diabetes, azoturia and creatinuria were only restrained during the period of activity of the dose of insulin injected. Therefore, it appears that when exclusive dependence is placed on multiple doses of an insulin which has an action of short duration, intervals may occur in each 24 hours when the balance for nitrogen will be negative. If unmodified insulin is used this can only be prevented by spacing doses more closely than has been customary. Such periodic intervals of azoturia are not encountered when an insulin is used which has an activity extending for more than 24 hours, and I have suggested that the continuous protection of the proteins of the tissues affected by this means may account for the improved healthiness and apparent gain of tolerance of patients using protamine insulin.

Finally, I also have directed attention to the usefulness of protamine insulin in the treatment of diabetic acidosis. Here again, its value seems to depend on the continuity of the insulin activity obtained.

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THE HEMOPOIETIC LIVER PRINCIPLE*

By G. E. WAKERLIN, M.D., Ph.D., F.A.C.P., *Louisville, Kentucky*

THE hemopoietic liver principle is also known as the anti-pernicious anemia principle and the erythrogenic liver principle. As you are aware, the interaction in the gastrointestinal tract of an as yet unidentified constituent of the gastric juice, called the "intrinsic factor," with some dietary component associated with protein, known as the "extrinsic factor," forms a third substance which is absorbed via the portal circulation and stored in the liver where it is very likely further elaborated. This substance, the hemopoietic liver principle, is then released to the bone marrow where it brings about the normal maturation of the red blood cells from the megaloblastic to the normoblastic stage. The term, anti-pernicious anemia principle, implies that the substance is pharmacologic rather than physiologic in character. Furthermore, the principle is effective in the treatment of various macrocytic, hyperchromic anemias other than pernicious anemia. The term, erythrogenic liver principle, is too limited inasmuch as the substance also appears to stimulate the formation of granulocytes and thrombocytes, as well as the maturation of the red blood cell. Hence the term, hemopoietic liver principle, appears to me to be the most appropriate. In this discussion, I shall deal briefly with some features of the chemistry, bioassay, physiology and pathological physiology of the hemopoietic liver principle.

Since the demonstration of the effectiveness of liver in pernicious anemia by Minot and Murphy [1] in 1926, the chemistry of the hemopoietic liver principle is being slowly unfolded. As a result of the early work of Cohn and his coworkers [2] in 1927 leading to the preparation of a potent liver extract suitable for oral administration, it became apparent that the hemopoietic principle was relatively heat-stable, soluble in water and 70 per cent ethanol, relatively insoluble in 95 per cent ethanol, and insoluble in ether. In 1928 Cohn [3] further purified his liver extract so that 0.6 gm. per day orally was as effective as 250 gm. of whole liver in the treatment of pernicious anemia. At this time, Cohn considered the active principle to be either a nitrogenous base or a polypeptide. In 1930, Gänsslen,[4] Cohn,[5] and Castle [6] prepared liver extracts of sufficient purity to be administered parenterally. Cohn then regarded the hemopoietic liver principle as a secondary or tertiary amine. In 1935, Dakin and West [7] prepared the principle in such form that 80 mg. parenterally was effective in producing a remission in pernicious anemia patients. They considered the active principle to be a complex consisting of an aminohexose or glucosamine and certain amino-acids. Pyrimidine and purine bases were absent according to them. In the same year,

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From the Department of Physiology and Pharmacology, University of Louisville School of Medicine.

Fiske and his coworkers [8] reported that the hemopoietic principle was probably a combination of l-tyrosine, a complex purine, and a third unidentified fraction. In 1936, Dakin and his collaborators [9] modified their previous conception somewhat and reported that the principle was a peptide containing arginine, leucine, glycine, proline, hydroxy-proline, aspartic acid, and an acid resembling hydroxy-glutamic acid. In the same year, Wilkinson [10] reported the preparation of the principle in such form that 18 mg. was sufficient to produce a remission in pernicious anemia and Strandell, Laland, and their coworkers [11, 12] stated that they had a product which was effective in the astoundingly small dose of 0.7 mg. Neither of these groups of investigators gave any data on their conceptions of the chemical structure of the hemopoietic principle. The chemistry of the principle, therefore, is still unsettled, although as indicated, there has been considerable progress. Very little is known about the chemistry of the two precursors of the hemopoietic principle. The intrinsic factor of the gastric juice is probably enzymic in nature; it is heat-labile, and otherwise different from the liver principle.[13] The so-called extrinsic factor of the dietary likewise has not been identified chemically as yet but it is known to be relatively heat-stable and to be associated with protein, especially that of beef muscle, autolyzed yeast, eggs, rice polishings, wheat germ, and liver.[14] Although it was once thought that the extrinsic factor was vitamin B_2 (G), this is now definitely known not to be the case.[15, 16]

Since the hematogenic liver principle cannot be tested for chemically, preparations thought to contain it must be assayed biologically. Up to the present, the only satisfactory assay subject is the untreated pernicious anemia patient showing a red blood cell count of 3,000,000 or less.[17] After a control period of 1 to 7 days, the material to be tested is administered during a 10-day interval and daily reticulocyte counts together with erythrocyte, hemoglobin and leukocyte determinations every two to three days are made. The presence of satisfactory quantities of the hemopoietic liver principle in the preparation assayed is shown by a temporary reticulocytosis reaching its peak on the fifth to the eighth day and an accompanying or succeeding increase in erythrocytes and hemoglobin. The minimum reticulocyte response to be expected with a potent preparation is to a certain extent inversely proportional to the original level of the red blood cells. The standard minimum reticulocyte responses are as follows: for a level of 1,000,000 red blood cells per cu. mm., 30 per cent; 1,500,000, 18 per cent; 2,000,000, 12 per cent; 2,500,000, 7 per cent; and 3,000,000, 4 per cent. However, during the past few years, the use of this method of clinical assay has become increasingly difficult owing to the scarcity of untreated patients with pernicious anemia. Moreover, work on the chemistry and physiology of the hemopoietic principle and on the pathogenesis of pernicious anemia and other macrocytic, hyperchromic anemias has been greatly impeded. Hence numerous attempts have been made to devise a suitable laboratory method of bioassay. Of the many procedures proposed, the so-called guinea

pig,[18, 19] rat,[20] and pigeon [21] methods have received most attention. Each of these depends upon the production of a significant reticulocytosis in normal members of these species by the administration of material containing the hemopoietic liver principle. The validity of each of these methods has been questioned especially on the ground that the reticulocytoses regarded as significant are actually within the limits of normal variability. Certainly the magnitude of the reticulocyte increases regarded as significant by the proponents of the guinea pig and rat methods are very small. Recently we have modified the original pigeon method in such a way as to overcome the objections which have been raised against it.[22] Unfortunately, however, we have found that the reticulocytosis produced in pigeons by the hemopoietic liver principle is not specific for this substance. This same objection of non-specificity applies equally forcibly to the guinea pig and rat methods. Our modification of the pigeon method, however, is of definite value as a negative test and further work with liver preparations of known effectiveness or ineffectiveness in pernicious anemia may well show it to be of value in a positive way as well. The ideal laboratory bioassay procedure, of course, involves the production of experimental pernicious anemia, or at least a readily obtainable, chronic, and reasonably severe macrocytic, hyperchromic anemia in animals. Although I shall speak later of experimental macrocytic, hyperchromic anemias produced in animals, difficulties of a practical or other nature appear to preclude the utilization of any of those produced thus far for assay purposes.

Having considered the chemistry and bioassay of the hemopoietic liver principle, we now pass to a consideration of certain facts known concerning its physiology and pathological physiology. Subsequent to the demonstration by Minot and Murphy of the effectiveness of liver in the treatment of pernicious anemia, Castle and his coworkers [23] in 1928 showed that whereas normal human gastric juice mixed with beef muscle was, like liver, effective in the treatment of pernicious anemia when administered orally, a mixture of beef muscle and gastric juice from patients with pernicious anemia was ineffective. Despite some contradictory findings, subsequent work by others has amply confirmed Castle's conclusion that by the interaction of the so-called intrinsic factor of the gastric juice and the so-called extrinsic factor of the dietary, there is formed in the upper gastrointestinal tract of the normal individual a third substance which is absorbed by way of the portal circulation and stored in the liver. From there, probably after further elaboration, the hemopoietic principle is released by way of the blood and passes to the bone marrow to exercise its characteristic effect in facilitating the maturation of the red blood cells from the megaloblastic to the normoblastic stage. Due to the comparative absence of the intrinsic factor in the gastric juice in pernicious anemia, the physiologic process just outlined is grossly deficient and as a consequence normal hematopoiesis is depressed with the resulting macrocytic, hyperchromic anemia, granulopenia, and thrombopenia characteristic of this disease. Whereas normal hog, dog,

beef, and human livers have been shown to contain appreciable quantities of the hemopoietic principle, the livers of untreated or inadequately treated pernicious anemia patients have been found to be devoid or nearly so of this substance.[24, 25] Obviously, if the physiological cycle outlined for the hemopoietic liver principle is correct, interference with its normal sequence in other ways should result in a macrocytic, hyperchromic type of anemia. (1) Thus one might expect that gastrectomy would lead to a pernicious anemia-like blood-picture. However, complete gastric resection in the rat,[26] hog,[27, 28] dog,[29] and monkey [30] has led only to a mild microcytic, hypochromic anemia in the hands of all investigators except one,[31] although the amount of the hemopoietic principle in the liver of the hog has been shown to decrease following gastrectomy.[27, 32] The explanation of these essentially negative results is not entirely clear but the fact that the intrinsic and extrinsic factors have been shown to be present not only in the wall of the stomach but also in the wall of the duodenum [33, 34] and probably the jejunum, ileum,[35] and colon of the hog may well be important in this connection. On the other hand, a macrocytic, hyperchromic anemia resembling that of pernicious anemia develops in a definite percentage of humans subjected to complete gastrectomy for carcinoma or other causes and is relieved by the administration of the hemopoietic liver principle.[36] (2) A lack of the extrinsic factor in the diet should result in a deficiency of the hemopoietic liver principle. Thus far the difficult task of devising a diet free of the extrinsic factor and feeding it to animals has not been reported. However, a vitamin B_2 deficient diet which was probably also deficient in the extrinsic factor, has been shown to produce a macrocytic anemia in approximately half of the hogs to which the diet was given. Moreover, the intrinsic factor was reported to have disappeared from the gastric juice of the anemic animals.[37] A macrocytic anemia in monkeys on a vitamin B_2 deficient diet, probably lacking in the extrinsic factor, has also been reported.[38] Clinically a dietary lacking in the extrinsic factor appears to be one of the factors involved in the genesis of the macrocytic anemia which may occur in sprue.[39] It is likely also that a deficient intake of the extrinsic factor is responsible for tropical macrocytic anemia, in which treatment with either the extrinsic factor or the hemopoietic liver principle is effective.[40] (3) Deficient absorption of the product of the interaction of the intrinsic and extrinsic factors should also produce a blood-picture resembling pernicious anemia. Experimentally, a macrocytic, hyperchromic anemia has been produced in dogs by stricturing the small intestine and thus, according to one interpretation, producing changes in the intestinal wall which interfere with the absorption of the hemopoietic principle.[41] Clinically, macrocytic anemia may appear in sprue, ileitis,[42] and patients with intestinal strictures [43] or gastro-colic fistulae [44] where the absorption of the hemopoietic substance is undoubtedly interfered with, and in such patients parenteral therapy with the hemopoietic principle is of value in removing the anemia. (4) Sufficiently severe damage to the liver with resulting inade-

quate storage and elaboration of the hemopoietic principle should also produce a pernicious anemia-like blood-picture, if the physiological cycle outlined for the hemopoietic principle is correct. Experimentally, the repeated administration of large doses of carbon tetrachloride to dogs and rats with a consequent severe chronic liver damage and cirrhosis has led to the appearance of a macrocytic, hyperchromic anemia in some of the animals.[45] The same result was obtained in a few dogs by gastrectomy followed by carbon tetrachloride administration.[46] Clinically, there are many reports of macrocytic, hyperchromic anemia occurring in patients with cirrhosis of the liver [47, 48, 49] and very probably some degree of macrocytosis occurs in nearly all patients with advanced diffuse liver disease.[50, 51] Moreover, assay of the livers of patients with cirrhosis and a pernicioid blood-picture has shown such livers to be deficient in the hemopoietic principle and the administration of the principle is effective in relieving the anemia in some of these patients.

We shall now consider data on two other points relative to the physiology of the hemopoietic principle. These involve its storage in sites other than the liver and its excretion. (1) Thus far the liver is the only proved site of detectable quantities of the hemopoietic principle. Dried, defatted hog stomach, duodenum, and probably jejunum, ileum, and colon are effective in the treatment of pernicious anemia when administered orally not because they contain the hemopoietic liver principle but because they contain its two precursors, the intrinsic and extrinsic factors. Salivary glands [9] and muscle do not contain the liver principle. Neither do saliva,[52] gastric juice,[53] or duodenal juice,[52] although some workers have claimed that gastric juice does.[54, 55] Kidney,[56] brain,[57] and pancreas have been shown to be effective in pernicious anemia when administered orally. Kidney is as effective as whole liver by mouth, whereas brain and pancreas are approximately one-third as effective. What the active materials in these organs are and what relation they have to the hemopoietic liver principle are not completely apparent at present. In the case of the kidney and brain, however, Dakin, Ungley, and West [9] have presented strong evidence that the potent substance is not the hemopoietic liver principle, inasmuch as extracts of kidney and brain prepared by methods yielding potent parenteral liver extracts were ineffective parenterally in pernicious anemia. Recently we obtained similar results with kidney.[58] (2) In view of the fact that the hemopoietic liver principle undoubtedly passes to the bone marrow via the blood stream, we examined normal human urine for the possible presence of the substance. First we found normal human urine to be reticulocytogenic for the pigeon similarly to liver extract.[59] Other investigators have reported like findings using the rat [60] and guinea pig.[61] We then prepared an extract of urine by a method basically that employed in making liver extract and found the urinary extract to be reticulocytogenic for the pigeon. In the cruder chemical properties of solubility and relative heat-stability the reticulocytogenic urinary principle resembled the hemopoietic liver principle. However, in view of the non-specificity of the pigeon method of assay, the urinary

extract was then studied in pernicious anemia patients. Negative results in three patients showed definitely that the urine principle is not the hemopoietic liver principle.[58] The hemopoietic principle, therefore, is not excreted as such in detectable quantities in the urine. Just what the relation of the reticulocytogenic urine principle to the hemopoietic liver principle is cannot be stated at present, although we are inclined to consider the former a decomposition product of the latter.

In this brief discussion I have attempted to summarize for you certain features of our present knowledge of the chemistry, bioassay, physiology, and pathological physiology of the hemopoietic liver principle. As you have gathered, this knowledge in many respects is incomplete. However, as our knowledge of the principle increases, many of the present obscurities in the physiology of hematopoiesis and in the pathogenesis of certain of the blood dyscrasias will be swept away.

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THE HEMATOPOIETIC RESPONSE FOLLOWING ORAL ADMINISTRATION OF DESICCATED DUODENAL MUCOSA *

By JOHN C. THOMPSON, F.A.C.P., *Lincoln, Nebraska*

THE fundamental work of Castle and his coworkers [1, 2, 3, 4] proving that a definite antianemic substance, "Intrinsic Factor," is produced in the wall of the stomach, at present seems to be established beyond a reasonable doubt. The theories developed by the author on the basis of this monumental discovery have, however, been questioned by a number of observers. Some of these objections, notably those of Greenspon,[5] have had to do with the nature of the antianemic material and the method of its production in the stomach. A more serious discrepancy, however, exists in the theory that this vital material is developed only in the stomach and stored in various other structures of the body. It is the purpose of this paper to offer some facts to prove that this assumption is incorrect and that antianemic material is also produced in other portions of the gastrointestinal tract.

From a clinical point of view the fact that complete or at least extensive gastrectomy does not promptly produce the picture of a primary anemia should at once cast a reasonable doubt on the completeness of Castle's hypothesis. In 1933 Roeder [6] collected from the literature the clinical records of 88 cases of complete removal of the stomach while Goldhamer [7] in the same year following a similar search discovered only 23 cases of severe anemia following this operation. In Roeder's report reference was made to a case of A. W. Mayo Robson's living and in apparently good health 30 years following an almost complete gastric resection. Cases reported by Walters,[8] Judd and Marshall,[9] Clute and Mason,[10] Morrison,[11] and others failed to exhibit any sign of pernicious anemia at intervals varying from several months to years following their operation. Poole and Foster's [12] case lived for three years following a complete gastrectomy without noticeable blood changes, then developed a pernicious anemia which responded well to appropriate treatment. These latter authors expressed the view that in any instance complete removal of the stomach would eventually lead to the development of an Addisonian type of anemia if the patient's postoperative life was sufficiently long.

In his 23 cases Goldhamer found only one individual in whom the anemia appeared as early as the fifth month; in the others it came on at intervals varying from one to 15 years. From this observation he concluded that the time element was an important factor in the development of the condition.

On the experimental side Ivy, Morgan, and Farrell [13] reported in 1931, after a study extending over a period of seven years, that of 14 gastrectomized dogs, living for six months or longer following operation, three

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developed a spontaneous anemia, and three were anemic only during pregnancy. The anemia observed was of secondary type and was responsive to treatment by iron. This work was confirmed by Mullenix, Dragstedt, and Bradley [14] in 1933, and by Dragstedt, Bradley, and Mead [15] in 1935. Maison and Ivy [16] in 1933 reported similar observations on swine and suggested at this time that an intestinal factor might be the cause of their failure to produce a macrocytic hyperchromic blood picture. Judd and Marshall in their report on gastric resection stated that Mann had three dogs living over four years following gastrectomy, in good health and without anemia.

A study of the cases collected by Goldhamer and others is of especial interest in view of the results of the experimental physiologists, for it is quite apparent that at least some of the clinical records do not contain a sufficient amount of evidence to establish clearly a diagnosis of pernicious anemia and it is quite possible that some of these individuals suffered with the same hypochromic, iron requiring anemia which proved fatal in some of the experimental animals. It is further to be noted that a number of the dogs operated upon experimentally, lived for years without developing a primary anemia. This would add some color to the views expressed by Poole, Foster and Goldhamer to the effect that time is an essential element in the development of the condition. While this premise is doubtless true their implied explanation cannot be accepted, for it is illogical to assume that the vital antianemic material is produced only in the stomach, and stored in the liver or other tissues in such inexhaustible quantities that its presence in effective amounts would be felt for months or even years after its source of renewed supply was completely abolished.

Further study of gastric secretion has also brought to light certain facts not adequately explained by Castle's postulates. This author in his investigation of two individuals suffering with typical Addisonian anemia but with apparently normal gastric juice found that the intrinsic factor was absent. In one individual with complete achylia but without anemia and in three persons suffering with anacidity and hypochromic anemia he found the material present. On the contrary Barnett [17] in 1931 reported two cases, one of sprue, and the other with a typical pernicious anemia, both of whom had normal gastric secretions containing a sufficient amount of intrinsic factor to produce a remission in an untreated case of the latter disease. In 1932 Barnett [18] published a report concerning several cases of anacidity in which the intrinsic factor was missing but the individuals exhibited no signs of anemia. In 1935 Goldhamer, Isaacs, and Sturgis [19] found that the gastric secretion of untreated cases of pernicious anemia contained appreciable quantities of intrinsic factor. They were able to demonstrate a definite relationship between the volume of gastric juice found in the stomach and the erythrocyte level in the usual case suffering with the disease. They also discovered that the average volume of gastric secretion was 20 c.c. per hour in the anemic individuals whereas normal persons produced 150 c.c. per hour. Their work would imply that a re-

duction in volume of gastric secretion would necessarily reduce the available supply of intrinsic gastric factor. Yet, Bloomfield and Polland [20] found after a study of 45 cases of anacidity, extending over a period of one to seven years that not one of these individuals had developed a pernicious anemia. This group included two of the cases previously reported by Barnett in 1932 in whom the intrinsic factor was absent. At present these separate facts taken from the literature might be considered to be controversial in character and in the light of Greenspon's recent observations it is possible that failure to take into account peptic activity may have influenced the results obtained by various observers. There is suggested, however, from these experiments a possibility that intrinsic factor may be derived from other sources than the stomach. If the latter assumption is true then the cases first reported by Barnett were anemic because the unknown source of intrinsic factor was exhausted and the gastric supply was insufficient to handle the situation. In the cases of anacidity later reported by Barnett, Bloomfield, and Polland anemia did not occur in the absence of intrinsic gastric factor for the reason that the unknown source adequately met the requirement for blood regeneration. The observations of Goldhamer, Isaacs, and Sturgis would suggest that if in the ordinary case of pernicious anemia the erythrocyte level paralleled the volume secretion of the stomach that in such usual cases the output of the second unknown source of supply must necessarily rise and fall with the volume production of the stomach. This would not only imply that the development of intrinsic factor is a quantitative reaction but would suggest some close physical relationship between the stomach and this as yet unrecognized source.

The idea that the gastrointestinal tract might provide a source of intrinsic factor production other than the stomach was discouraged by the original contribution of Castle who reported that this material was not demonstrable in normal human saliva or duodenal contents free from gastric juice. On the contrary Maison and Ivy in their work on swine suggested that an intestinal factor might enter into their failure to produce the hyperchromic blood picture. From the pathological view point Brown [21] in a discussion of the pathology of pernicious anemia pointed out the frequent occurrence of lesions in the small intestine while the literature on the subject of tropical and non-tropical sprue has contained frequent reference to the presence of intestinal pathologic alterations.

From a clinical and experimental aspect the literature is not devoid of material suggesting the possibility of an intestinal factor in the production of hyperchromic anemia. In 1927 Seyderhelm, Lehman, and Weichels [22] reported that a pernicious anemia-like blood picture occurred in dogs after experimental stricture of the small intestine. In 1929 Little, Zerfas, and Tressler [23] reported a clinical instance of pernicious anemia following lateral anastomosis and chronic small intestinal obstruction in man. During the same year Meulengracht [24] found 21 similar cases in the literature and reported another. In 1936 Hawksley and Meulengracht [25] reported still

another case and found that a total of 24 had made their way into the literature up to that time.

At present Castle's postulate, to the effect that a lack of intestinal absorption of potent anti-anemic material is responsible for the development of certain cases of primary anemia, has been accepted as an explanation for the development of hyperchromic anemia in the above mentioned cases of intestinal stricture as well as in cases of idiopathic steatorrhea and sprue. It is, however, just as reasonable to assume that the blood picture in these conditions is due either partially or completely to a failure of the small intestine to produce in adequate amounts its share of the required intrinsic factor. If the latter assumption is correct then the frequent incidence of anacidity and disturbed gastric secretion in cases such as those cited above has a real significance for we must conclude then that primary anemia is essentially a condition produced by a definite quantitative loss of intrinsic factor production in both the stomach and intestine. Such a conclusion provides a more reasonable explanation for the results of experimental and clinical gastrectomy, for if the appearance of primary anemia is the result of the loss of a definite quantity of intrinsic factor produced in both the stomach and bowel the delayed development of this anemia must be due to gradually developing pathological changes in the intestinal mucosa and a destruction of its capacity to produce antianemic material. In this connection it must be emphasized that Castle's hypothesis assuming that all precursor substance arises in the stomach excludes any question of intestinal absorption in the cases of total gastrectomy for the reason that with intrinsic factor absent there should be nothing to absorb.

With this theoretical background it yet remains to offer some substantial proof that intrinsic factor can be and is developed in the intestinal tract. As was previously stated, Castle in 1928 found that antianemic activation of meat did not occur with duodenal secretion. In 1933 Kuehnau [26] carried out a number of feeding experiments which suggested that intrinsic factor was present in the duodenal juices. His work, however, was open to criticism for he employed a mixture of duodenal and gastric secretions. In 1935 Meulengracht [27] reported positive results in the treatment of primary anemia with duodenal mucosa, while Cheney [28] in 1936 discovered that liver extract incubated with duodenal mucosa produced an anti-anemic material of potency equal to or greater than that of the commercial product "Extralin" developed in similar fashion by the incubation of liver with stomach mucosa.

The present work was undertaken in January 1935 and has been carried on continuously for a period of two years. During this interval a number of individuals suffering with pernicious anemia in relapse and various other anemic states have been given a preparation of desiccated duodenal mucosa with results which indicate the presence of a potent anti-anemic substance in the duodenum. The material used in this experimental work has been generously provided by the Research Division of the Eli Lilly Co., and has

been prepared by the usual methods of desiccation from the duodenal mucosa of swine. Each gram of the finished product has represented 4.5 grams of raw substance.

Case Reports

Case 1. Pernicious anemia in relapse.

History: The patient, Geo. C. L., aged 66, carpenter, was seen on July 19, 1935, complaining of anemia, weakness, dyspnea on exertion, dull aching in the chest, palpitation of the heart, swelling of the feet and ankles, numbness and tingling in the hands and feet, dull aching in the limbs after a short walk, abdominal distress, slow stream and dribbling of urine. Some of these symptoms dated back to 1921 when a diagnosis of pernicious anemia had been made. During that year the anemia had been so severe that transfusion was done. Occasional relapses then occurred requiring transfusion until the advent of the liver diet.

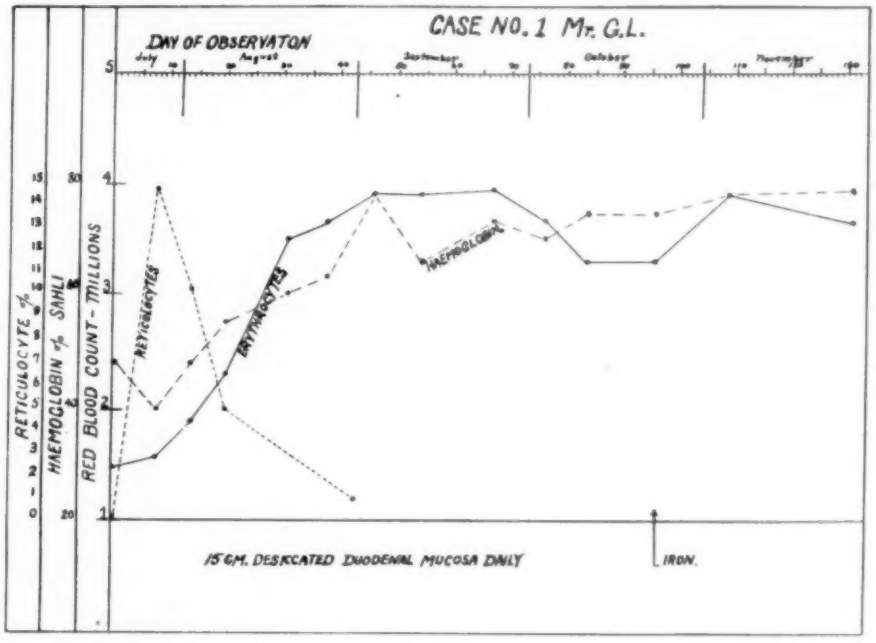

Fig. 1.

In July 1929 an office record indicates that he had been unable to work for a period of seven months because of weakness, numbness in the lower extremities, etc. Salient points of the examination at the time were: A lemon yellow pallor of the skin; red blood cells 2.62 millions; a systolic murmur at the cardiac apex; normal heart boundaries; blood pressure 120 mm. of Hg systolic and 60 diastolic; liver edge just below the costal margin and a palpable spleen. Complete remission then occurred on Lilly's Liver Ext. 343 in a dose of two vials three times daily. During the following years owing to financial difficulties the patient was able to maintain adequate treatment only at intervals and in consequence his erythrocyte level was subject to wide variations. On August 8, 1930, the red blood cells were 1.60 millions and the hemoglobin 35 per cent while on February 21, 1933, the red blood cells were 4.84

millions and the hemoglobin 82 per cent. Response to proper therapy during this interval, however, was always satisfactory. From February 21, 1933 on, a physician was not consulted until he presented himself for treatment on July 19, 1935 with the symptoms outlined above, most of which had been present for a considerable period of time.

Physical Examination: The patient was a moderately thin white male. Pulse 72. Temperature 98.6° F. Pupillary reactions were normal. Pyorrhea and recession of the gingivae were noted about the remaining teeth. The tongue was slightly coated but the papillae were still present and there was no evidence of glossitis. Mucous membranes were pale. The radial arteries were thickened. The heart was slightly wide at the base. The heart sounds were somewhat muffled, a roughness of the first sound was heard in the aortic area, and a systolic murmur, not transmitted, was present at the apex. The lungs were emphysematous and subcrepitant râles were heard on inspiration particularly over the bases. The liver edge was three fingers-breadth below the costal margin. The spleen was not palpable. The feet were cold and clammy and pulsation in the dorsalis pedis arteries could not be definitely palpated. Vibratory sense was somewhat questionable. Neurological examination otherwise was negative. The prostate was atrophic; its secretion contained considerable pus. Dorsal kyphosis with moderate limitation in movements of the spine was noted.

Laboratory Examinations: Upon roentgen-ray investigation the thoracic aorta was found to be slightly dilated and its shadow increased in density. The excursion of the diaphragm was limited and some infiltration was noted along the lower bronchi. The gastrointestinal tract was negative except for moderate ptosis.

The hemoglobin was 48 per cent (Sahli). The red blood cell count was 1.45 million. Volume index was 1.2. Reticulocytes were absent. Poikilocytosis and anisocytosis were noted as well as a very definite macrocytosis. The white blood cell count was 9,700 and upon differential count there were 40 per cent lymphocytes, 3 per cent monocytes, 4 per cent juvenile forms, 10 per cent rod forms and 51 per cent segmented cells. Of the latter, 34 per cent contained three or more divisions of the nucleus. The blood Wassermann test was negative. The stomach contents contained no free acid after histamine. Blood calcium was 9.5 mg. and phosphorus 3.2 mg. per 100 c.c. of blood. The bromsulphalein liver function test, at 5 minutes, showed 40 per cent retention of dye, at 15 minutes 25 per cent, and at 30 minutes none. Urine was negative.

Treatment and Progress. On July 19, 1935, the patient was placed on 15 gm. of desiccated duodenal mucosa, representing 72 gm. of raw material daily. This treatment was continued without interruption and with no other medication until September 11, 1935, a total of 54 days. The reticulocyte count increased from zero to a peak level of 14.8 per cent on the eighth day. The erythrocyte count changed from 1.45 million on July 19 to 3.9 million on September 3, a total of 46 days, and an average gain of 375,000 cells per week. Hemoglobin rose from a low point of 40 per cent to 78 per cent on September 3. Because of slight edema of the feet and ankles, a slight dyspnea on exertion, and some enlargement of the liver the patient was given digitalis in a dose of 4½ grs. of powdered leaf daily beginning September 11. This treatment has been continued at intervals. On October 23, 1935, a moderate dose of iron was prescribed. In December 1935 an investigation of the bladder for residual urine was negative. During the early months of 1936 the patient had an acute respiratory infection and some trouble with hemorrhoids requiring treatment. On March 30, 1936, the red blood cells were 4 million and hemoglobin 90 per cent. During the months of April, May, and most of June the patient did not return for observation and received no treatment. On June 27, 1936, the red blood cell count had dropped to 2.9 million and the hemoglobin to 64 per cent on December 9, 1936; on treatment the red blood cell count was 4.4 million and the hemoglobin 87 per cent.

The total period of observation in this case has been 18 months. During this interval the erythrocyte count has been maintained at a satisfactory level on relatively small amounts of desiccated duodenal mucosa and has dropped very definitely on one occasion when the patient failed to take this material over a considerable period of time. General health has been very much improved although some symptoms due to arteriosclerosis persist and are troublesome.

Case 2. Pernicious anemia in relapse.

History: The patient, Mrs. M. H., aged 47, was first seen on April 1, 1936. The major complaints at the time consisted of a feeling of fatigue and weakness, and a numbness in the hands and feet. The latter symptom was so severe that the patient lacked definite control of her extremities. She could not walk in the dark without assistance, and she frequently dropped dishes and other objects from her hands. She had experienced a soreness of her tongue at its tip and edges at intervals for three years. She suffered with anorexia, nausea, salivation, flatulence and constipation. She complained of a low backache, nervousness, and leukorrhea. The development of these symptoms had occurred over a period of months to years. The menopause had occurred three years previously. History in all other respects was essentially negative.

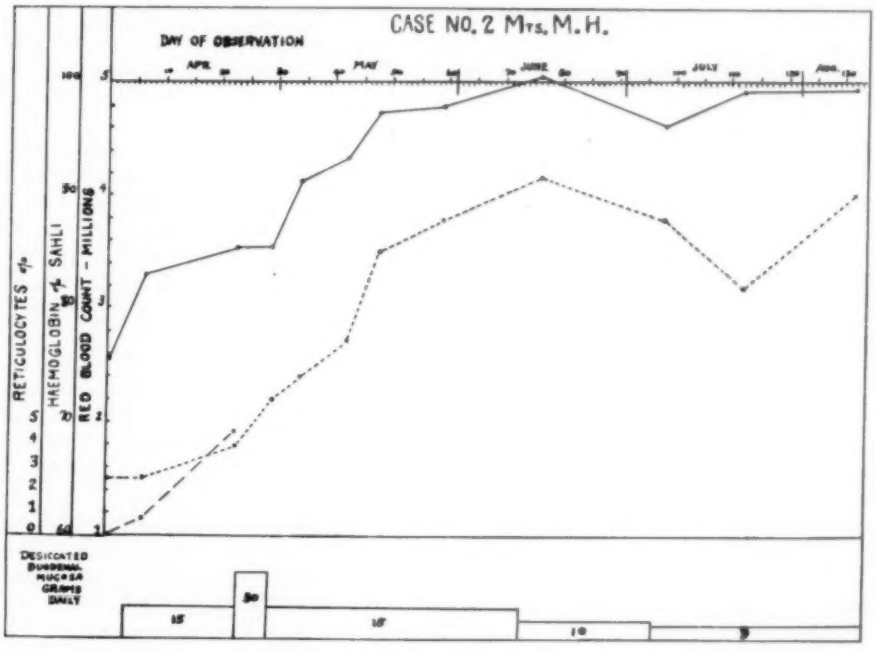

FIG. 2.

Physical Findings: Upon physical examination temperature was 99.5° F., pulse 76, and weight 10 pounds over optimum normal. The skin had a distinctly lemon yellow color. The mucous membranes were pale, and the sclerae pearly white. The tonsils were chronically inflamed. Considerable pyorrhea and gum recession were noted. The papillae of the tongue were not atrophic but patchy reddened areas

occurred along its edges. A cystic type of goiter was present of moderate size. The heart and lungs were negative. Blood pressure was 108 systolic and 74 diastolic. The abdomen was negative except for the presence of a spastic palpable sigmoid and moderate tenderness in both lower quadrants. Pelvic examination was negative. The knee jerks were sluggish. Plantar reflexes were normal. Epicritic sensibility was diminished and vibratory sense was absent. Romberg's sign was questionable. Hypertrophic changes were noted in the terminal interphalangeal joints.

Laboratory Data: The laboratory data were as follows: Erythrocytes 2.5 million; hemoglobin (Sahli) 65 per cent. Volume index 1.2. Color index 1.3. White blood cells 3700. A definite macrocytosis was present with anisocytosis and poikilocytosis. The differential count was lymphocytes 64 per cent, monocytes 2 per cent, stab forms 10 per cent, segmented cells 24 per cent. No free acid was present in the stomach contents after histamine. The stool contained no blood, ova, or parasites. The blood Wassermann was negative. Blood calcium was 11.5 mg. per cent. Basal metabolic rate was plus 11. Urine was negative.

Treatment and Progress. A diagnosis of pernicious anemia was made and treatment was started on April 4, 1936. The patient was given desiccated duodenal mucosa in a dose of 15 gm. daily from April 4 to April 24. During this interval a gain of 940,000 cells occurred or an average weekly increase of 329,000. On April 24 the dose was increased to 30 gm. daily for a few days followed by a daily administration of 15 gm. daily until June 15. The blood picture had returned to practically a normal condition on May 18, a total of 44 days. On June 15 the dose was reduced to 10 gm. daily. The average quantity consumed daily between the dates of July 6 to September 23, 1936, was 9 gm. No other therapy was advised with the exception of rest during the early phases of treatment and dental therapy which was started on May 28.

Upon the date when treatment was instituted the patient was hardly able to be up and about. Gastrointestinal complaints had disappeared by April 24 and the blood counts had returned to normal by May 28. The patient at this time was doing all of her own work. By July 21 she had very little complaint with reference to paresthesias and was scrubbing, washing, ironing and doing a large amount of hard work each day. The patient was last seen on January 18, 1937, at which time in spite of rather small dosage her erythrocytes were 4.4 million and hemoglobin 97 per cent. She had no complaints at this time.

Case 3. Pernicious anemia in relapse.

History: The patient, Mrs. W. C., aged 81, entered the Lincoln General Hospital on March 19, 1936, complaining of nocturia, diurnal frequency, and pain in the upper right quadrant. These symptoms had confined the patient to her bed for two weeks. In addition she had suffered with weakness and fatigue for six months, anorexia for four months, numbness in the hands for four months, slight dyspnea for years, and moderate edema of the feet and ankles. Coincident with urinary symptoms the patient had also suffered with pain and distress in the right flank and right upper abdomen.

Examination: The patient was well nourished. Temperature 98° F., pulse 84. The skin had a definite lemon yellow color and the sclerae were pearly white. The tongue was smooth and areas of redness were found along the edges. The heart boundaries were normal. The peripheral arteries were not sclerosed. A systolic murmur was heard at the cardiac apex. A rather marked tenderness and rigidity were noted in the upper right quadrant and right flank. Vaginal examination was negative. A slight pitting edema was noted in the ankles. The knee jerks were sluggish. Vibratory sense was lost in the lower extremities. Plantar reflexes were normal.

Laboratory Data: The urine on March 19, 1936, contained considerable pus. The erythrocytes were 1.36 million and the hemoglobin was 38 per cent (Sahli). Volume index was 1.4. Reticulocyte estimation was 0.8 per cent. Macrocytosis, anisocytosis,

poikilocytosis, and polychromatophilia were present. The differential was lymphocytes 50 per cent, monocytes 2.5 per cent, metamyelocytes 1.5 per cent, eosinophiles 1 per cent, basophiles 0.5 per cent, segmented forms 44 per cent, stab forms 0.5 per cent. On March 21, the stomach contents contained no free acid. On March 24, a urine culture was positive for *Escherichia coli*. Intravenous pyelogram done on April 7 showed a normal kidney function with normal pelvis and ureters.

Treatment and Progress: Thirty grams of desiccated duodenal mucosa were given daily beginning on March 20, 1936, and continuing until the patient left the hospital on April 12. During this interval the erythrocytes increased from 1.36 million on March 19, 1936, to 1.59 million in four days, to 1.68 million in seven days, to 1.97 million in 13 days and 2.45 million in 20 days. Reticulocytes multiplied from 0.8 per cent on March 19 to 9.6 per cent 10 days later. Daily counts were not made and the

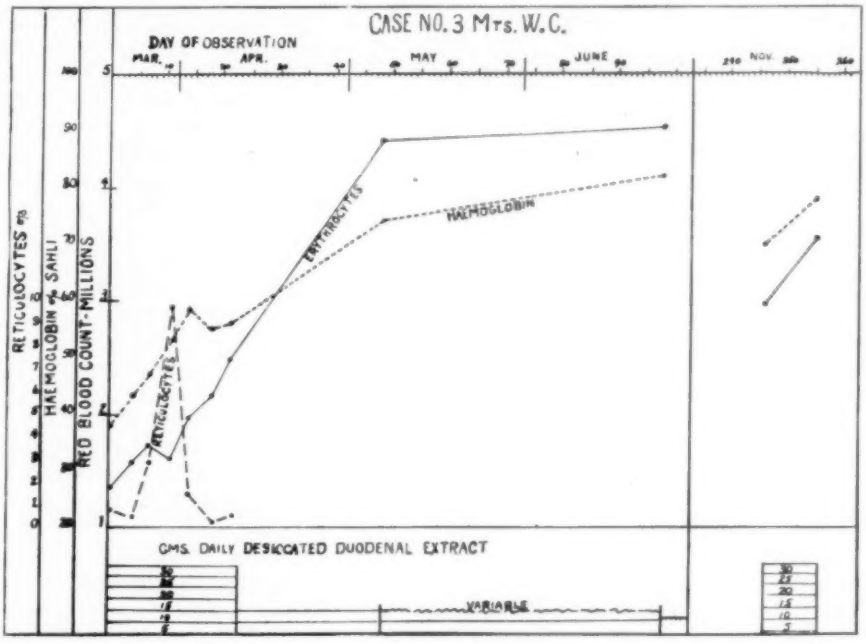

FIG. 3.

peak probably occurred prior to this day. Hemoglobin increased from 38 per cent to 56 per cent on April 9. A diagnosis of a right infected hydronephrosis was made which was thought in turn to be possibly due to a cord bladder. Treatment for this condition consisted of bed rest, urinary antiseptics, nitrohydrochloric acid, bladder catheterization and lavage. The infection cleared up promptly.

On the twenty-third day the patient was discharged from the hospital in very good condition with a supply of desiccated mucosa and a request to report at frequent intervals. Instructions were given to take 15 gm. of the material daily but the dose was reduced and the patient did not return until May 6. On this, her forty-seventh day of treatment, the erythrocytes were 4.4 million and the hemoglobin was 74 per cent. The increase of red blood cells for the 47 day period amounted to 3.05 million or an average per week of 450,000 cells. At this time the patient was not only doing some housework but was also spending some time in her garden.

In spite of a warning the patient continued to be careless in her attitude toward the use of antianemic material. Between the dates of June 19 and September 11, she

consumed a total of 540 gm. or a daily average of 6 gm. After September 11 she had no treatment until she finally returned on November 20, 1936. At this time she had no particular complaints. She had suffered with no recurrent abdominal distress or urinary symptoms and her urine contained no pus. Her erythrocytes, however, had fallen to 2.9 million and the hemoglobin was 70 per cent. She was again given 30 gm. daily and nine days later the erythrocytes were 3.57 million and the hemoglobin 78 per cent. Subsequent changes in the erythrocyte count are unknown for the patient left the city for the winter.

Case 4. Pernicious anemia with combined sclerosis of the spinal cord.

History: The patient, Mrs. F. W. J., aged 64, housewife, first presented herself for examination on January 24, 1935, with the outstanding symptom of abdominal distress. She stated that this trouble had been present for years and was accompanied by a severe constipation requiring constant catharsis, flatulence usually aggravated by cabbage, raw apples, etc., occasional passage of light colored stools, and pain of moderate severity usually felt in the lower abdomen but occasionally experienced above. She had been troubled with hemorrhoids, and bright red blood had appeared in her stools frequently over a period of 20 years. In addition she complained of weakness, nervousness, a numbness in the lower extremities present for the preceding five months, and a frequent soreness of the mouth which she described as canker sores. The latter had occurred over a period of at least four years. For years she had also been troubled by a loss of the sense of smell. This symptom had developed after a severe head cold. In other respects the history was essentially negative.

Physical Examination: The patient was 35 pounds under her normal weight. Temperature was 98° F., pulse 84. The examination of the head and neck was negative, excepting for the presence of several questionable teeth. Blood pressure was 164 systolic, and 96 diastolic. Peripheral vessels were normal. The heart was of normal size but a slight roughness of the first and a reduplication of the second tone were heard at the apex. The lungs were negative. A tenderness and a sense of resistance were noted in the upper right quadrant and the sigmoid was tender, spastic and palpable. The liver edge was slightly below the costal margin. The spleen was not palpated. Vaginal examination was negative. Upon inspection a number of inflamed hemorrhoids were noted. The knee jerks were sluggish. Circulation in the lower extremities was normal.

Laboratory Data (First admission): A non-functioning gall-bladder with gastroptosis, cecal stasis, and a slowing of the gradient through the large intestine was found on roentgen-ray examination. No free acid was present in the stomach contents either before or after histamine. The urine was negative. Icterus index was 10. Blood calcium was 8 mg. and phosphorus 3.2 mg. per 100 c.c. of blood. Hemoglobin was 85 per cent. Red blood cells were 3,880,000, and white blood cells 4700. Upon differential count the cells were classified as follows: Lymphocytes 60 per cent, monocytes 2 per cent, juvenile forms 6 per cent, stab forms 6 per cent, and segmented cells 26 per cent. Volume index was not done. A slight poikilocytosis was noted Blood Wassermann test was negative. The stool contained neither parasites nor blood but was thin as a result of catharsis.

Initial Treatment: Following this examination the patient was admitted to the Bryan Memorial Hospital and operated on February 18, 1935. The gall-bladder was found to be thick-walled, gray, and adherent to the duodenum. The appendix was retrocecal and adherent to the terminal ileum. Both were removed as well as three large, protruding internal hemorrhoids. The patient was discharged from the hospital on March 3, 1935, with no complaints and her strength rapidly improving.

History and Examination (Second hospital admission): The patient reëntered the hospital on May 23, 1935, with the statement that for one month after being discharged on March 3 she had noted a very definite improvement in strength and felt no paresthesias. At the end of this time, however, there gradually developed

a marked numbness with peculiar sensations of burning, and tingling in the hands and limbs, difficulty in walking, weakness, and an abdominal distress arising chiefly from constipation.

Upon examination the patient was undernourished, and unable to support her weight on her limbs. The tongue was very smooth. The abdomen was distended and the wall was thin. The knee jerks and tendo-achilles jerks were absent. The plantar reflexes were very sluggish. Both epicritic and vibratory senses were absent. Muscle strength in the limbs was fair but the patient was unable to stand or walk because of ataxia of the lower limbs. Finer movements of fingers and hands were also affected. Muscle sense in the limbs was impaired. On May 27 the erythrocyte count was 3.2 million and the hemoglobin 80 per cent. No reticulocytes were present. Volume index was 1.18. White blood cells, 5000. Poikilocytosis and anisocytosis were noted. Differential count was: Neutrophile rods 3 per cent, segmented cells 49 per cent, lymphocytes 46 per cent, and monocytes 2 per cent.

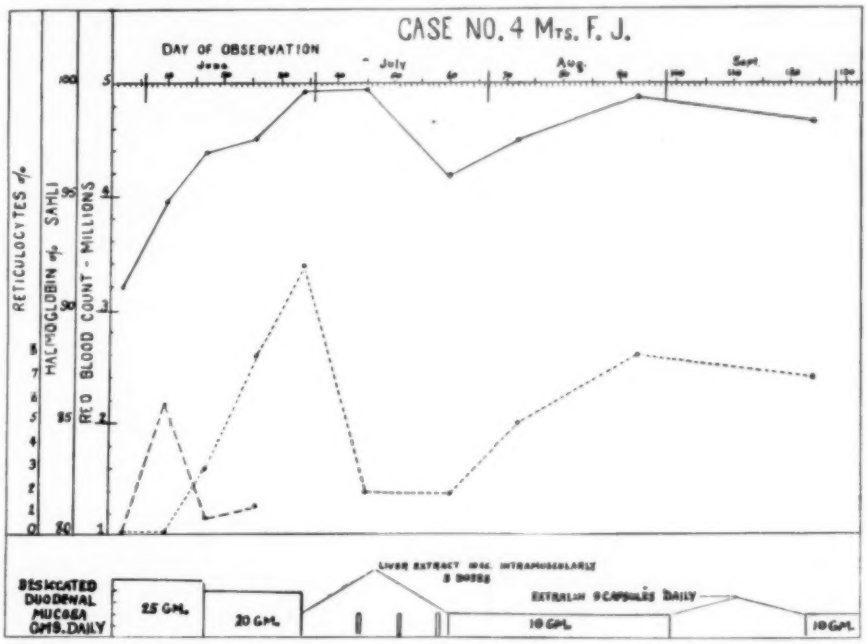

FIG. 4.

Treatment and Progress: On May 26 the patient was started on desiccated duodenal mucosa in a daily dose of 25 gm. After 17 days this dose was reduced to 20 gm. daily and continued for 17 days. At the end of 34 days the patient was tried at intervals on liver extract intramuscularly, extralin and later ventriculin. On each occasion, however, after a few days a definite loss of strength and an increase of symptoms were noted. A maintenance dose of 10 gm. of duodenal mucosa was started at the end of 60 days and has been continued with a few interruptions until the present time.

A definite improvement in symptoms was recognized as early as 12 days after the beginning of treatment. At the end of 32 days the patient was able to walk about her home and in her garden with the assistance of a cane. At the end of six months very little or no trace of the former ataxia could be noted. Knee jerks were sluggish but present. Epicritic sensibility had returned but vibratory sense was very

uncertain or absent. A very definite relief from digestive disturbances, particularly constipation was also observed on duodenal mucosa while the latter symptom was troublesome while taking ventriculin or liver.

On June 28, 1935, thirty-four days after treatment was started, the erythrocytes were 4.88 million and the hemoglobin 92 per cent. Since this time normal erythrocyte and hemoglobin levels have been obtained with the exception of moderate decreases occurring especially when treatment with other antianemic substances was utilized in probably inadequate dosage. A definite reticulocyte response occurred with a peak level of 5.9 per cent at the end of 10 days of treatment on desiccated duodenal mucosa.

Between the dates June 4 and October 2, a total of 120 days, the patient was given a daily ration of approximately 12 gm. daily. During this interval she maintained a normal erythrocyte count. During the following four months the patient's supply was curtailed and she was advised to use other anti-anemic substances. Whenever a supply was given to the patient during this interval she was required to appear for observation. This entailed a 70 mile auto trip which the patient on all occasions was eager to make for the reason that subjectively she repeatedly noted that she felt better and was stronger when taking desiccated duodenal mucosa.

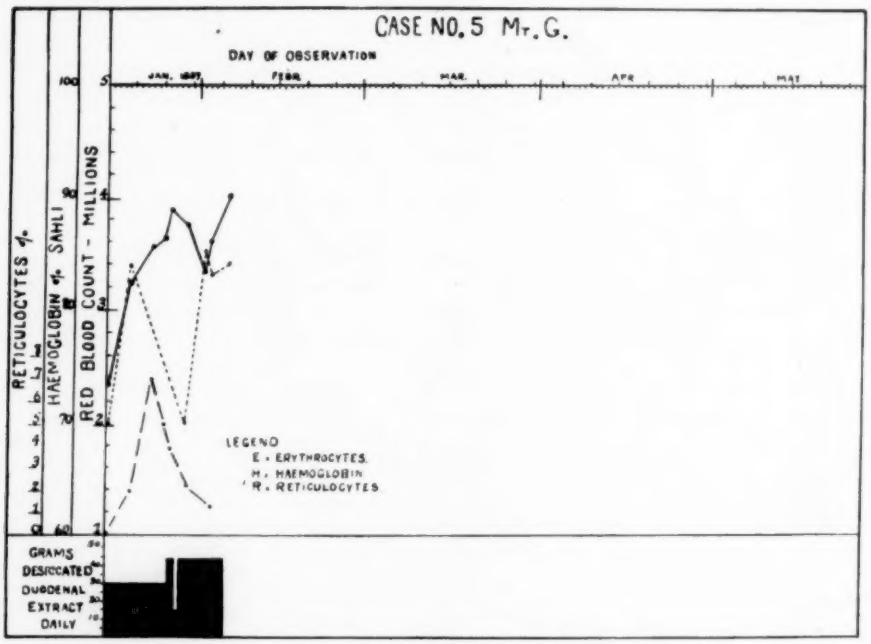

FIG. 5.

Case 5. Pernicious anemia with combined sclerosis of cord.

History: The patient, Mr. G., aged 53, store clerk by occupation, was first examined on January 14, 1937. He came in complaining of a stiffness in his legs and a feeling of tightness and pressure in the abdomen which he stated had been gradually developing over a period of months. He further complained of a wooden sensation in his hands and feet, a difficulty in walking in the dark, a sexual impotence of 6 to 7 months' standing, a lack of strength, constipation, flatulence, and abdominal distress. He had been unable to work for a period of six months. Past history was negative with the exception of a history of albuminuria 10 years previously.

Examination: Upon physical examination the weight was normal (178 pounds). Temperature was 99.2° F., pulse 64. A definite pallor was present. Sclerae were pearly white. The edges of the tongue were bald. The cardiovascular system was negative. Blood pressure was 140 systolic and 76 diastolic. The liver and spleen were not palpable. The abdomen was slightly tympanitic but otherwise negative. The testicles were atrophic. Neurological investigation revealed the presence of a positive Romberg, normal pupillary reactions, exaggerated knee jerks, and tendo-achilles jerks with normal plantar reflexes. Muscle sense was disturbed and a moderate loss of epicritic sensibility was noted in the lower limbs.

Laboratory Data: The laboratory data were as follows: Erythrocytes 2.2. million; hemoglobin (Sahli) 70 per cent; white blood cells 5500. Reticulocytes were absent. Anisocytosis, poikilocytosis, and macrocytosis were present. Volume index was 1.1 +. Differential count: Lymphocytes 28 per cent; stab forms 12 per cent; segmented neutrophiles 58 per cent; juvenile forms 2 per cent. No free acid was present in the stomach after histamine. Blood Wassermann was negative.

Treatment and Progress: On January 15, 1937, the patient was started on 30 gm. of desiccated duodenal mucosa daily. This dose was increased to 45 gm. daily on January 26, and with one interruption was continued until February 5, a total of 20 days. During this interval the red blood cells increased to 4 million, an average weekly increase of 600,000 cells. The reticulocyte count was probably not taken at its peak but was found at 7 per cent on the ninth day. During this interval the patient was not permitted to walk, but strength and color improved. Constipation was relieved as well as abdominal distress. Neurological changes in the lower extremities remained unchanged.

The red blood count on March 11, 1937 was 5,190,000, hemoglobin was 110 per cent and since this time the hemoglobin has never been below 100 per cent and the red count never less than 5,000,000 up to the present, June 23, 1937. Further, the patient is now able to walk without support of any kind for a considerable distance without tiring. There remains only a very slight feeling of stiffness in the limbs.

Case 6. Non-tropical sprue.

History: The patient, Mrs. C. P., aged 32, was first seen on April 24, 1934, complaining of diarrhea, gas, belching, bloating, cramping and abdominal distress, sore mouth and tongue, nervousness, fatigue, and heart burn.

She stated that her illness really started very insidiously while she was engaged in training for the vocation of nursing between the years of 1924 and 1927. During this interval her diet was extremely poor in general quality, contained very little meat, and consisted principally of starchy foods. The dietary habit so established was continued after graduation to a considerable degree and particularly so after a diagnosis of peptic ulcer was made in 1929.

Approximately five years previously the patient had rather suddenly developed a diarrhea associated with fever, and distress in the upper abdomen. She was suspected of having tuberculosis and was placed in bed for a period of six weeks. Fever subsided in six weeks but watery stools continued for six months. Since that time diarrhea had recurred two or three times each year and continued for intervals of six weeks to three months. At the height of this trouble as many as 10 to 12 stools were passed daily. In the intervals movements were normal. During the attacks of diarrhea the patient noticed a marked tendency for movements to occur between 4 and 5 a.m. causing a disturbance of rest and sleep. More trouble had been experienced in summer than during winter months.

Flatulence, bloating, and passage of large quantities of gas occurred at the onset and had continued to cause trouble. Rather marked distress was felt in the upper abdomen particularly in the first attacks. Tenesmus and pain accompanied this difficulty. In subsequent attacks these symptoms were not so severe. Heart burn had been present much of the time during the five year interval. Dilute hydrochloric acid

was tried for this trouble but it irritated the mouth and aggravated the symptom. In each attack of diarrhea a swelling of the lips and mucous membranes of the mouth had developed. There were also sores on the tongue which the patient described as not being the usual canker sore. Nausea and vomiting had occurred only at rare intervals and then only when some intercurrent infection was present.

Nervousness had been marked throughout the course of the illness. Limited strength and fatigue were early and persistent symptoms. The patient's strength was not sufficient to permit her to do her usual work and she was required to rest for at least two hours each afternoon. She had noted that fatigue seemed to aggravate her other troubles.

Upon further questioning it was found that the patient had never suffered with numbness, paresthesias, joint pains or muscle cramps. Insomnia had been experienced only to a slight degree.

Menses occurred at irregular intervals varying from 28 to 42 days. The flow was scanty and continued for five days. Pregnancy with death of one twin on delivery had occurred some two years previously. This had been followed by a severe attack of pyelitis. The history in other respects was negative.

Examination: (April 24, 1934). The patient's weight was 87¼ pounds. Height 60½ inches. Optimum weight 121 pounds. Temperature was 98.8° F., pulse 62. Blood pressure was 112 systolic and 86 diastolic. Patient's color was naturally dark, and an undue pigmentation of the face and arms could not be definitely determined. Head and neck were entirely negative except for a few palpable glands in the posterior triangles of the neck. The heart and lungs were negative. The abdomen was distended. The wall was thin, flabby, but symmetrical. Loops of bowel could be noted through the abdominal wall. There was no tenderness or other findings. No edema of the feet and ankles was present. A slight grating was noted in the left shoulder. Vaginal examination was negative. Proctoscopic examination revealed some muscular spasm in the pelvic colon and a slight irritation of the mucosa but no hemorrhoids and no cryptitis.

Laboratory Data: Upon radiological examination some calcification was noted in the right hilus with increased lung markings extending downward and outward from this area. The stomach was hyperperistaltic but otherwise negative. Barium lagged in the second and third portions of the duodenum and the normal markings of the *valvulae conniventes* were not present for some distance in the jejunum.

A number of stools examined were found to have the same general characteristics. They were of grayish color, soft consistency, foul odor, and contained a large amount of fat. Starch, muscle fibers, ova, parasites, pus, blood and mucus were absent. Occult blood was noted in traces.

The erythrocyte level on April 24, 1934, was 3.9 million, the hemoglobin was 74 per cent. Erythrocytes had a poor color, and were somewhat irregular in size. A definite macrocytosis was present. The white blood cell count was 4,200 and the differential count showed lymphocytes 46 per cent, juvenile forms 4 per cent, stab forms 4 per cent, and segmented cells 46 per cent. Definite deviation to the right was noted. The blood Wassermann test was negative. Blood calcium was 7 mg. per 100 c.c. of blood. Blood urea was 20 mg. per 100 c.c. On a fasting stomach, blood sugar was 89 mg. and rose to a maximum of 98 mg. in one hour after glucose ingestion. Stool culture on ordinary media was negative but was positive for a fungus on Sabouraud's media. Urine diastase was negative. Stomach acidity was within normal limits.

Treatment and Progress: The patient was placed on a practically fat free, high protein, and low carbohydrate diet. Later medication was given at intervals consisting of viosterol 10 ggt. three times daily, 2 c.c. of liver extract intramuscularly three times weekly, calcium lactate 10 gr. three times daily and still later ventriculin with

iron. On January 29, 1935, after nine months of the above treatment, the patient summarized her condition as very definitely improved but not satisfactory.

On January 30, 1935, the patient was placed on desiccated duodenal extract in a dose of 10 gm. daily. This was soon increased to 15 gm. and has been continued with a very few short interruptions for two years. During this interval the patient has had no other medication but has continued to observe the dietary program previously mentioned.

On January 29, 1935, the blood picture was as follows: Erythrocytes 4 million. Definite macrocytosis present. Reticulocytes 0.5 per cent, white blood cells 3,900. Differential count: Juvenile forms 10 per cent, monocytes 6 per cent, lymphocytes 40 per cent, rod forms 14 per cent, segmented cells 28 per cent, eosinophiles 2 per cent. On February 15, 1935, the erythrocytes were 5 million. This very definite improvement in the blood picture has been constantly maintained since that date. In the same 16 day interval the blood calcium and phosphorus also increased to normal levels and have been maintained with few interruptions. The stools have been free from an excess of fat except on a few occasions, particularly when the patient tried to take too much fat in her diet. On such occasions the stools have been loose and the blood calcium and phosphorus have also been found at lower levels. The symptoms of flatulence, abdominal distress, sore mouth and tongue, lack of strength, insomnia, nervousness, abnormal stools have not occurred for 18 months. The last difficulty occurred for a short period in June 1935. The patient has made a slow but steady gain in weight and her appetite is very good. She has been able to do her work without fatigue and is in better health than she has enjoyed for years. The patient was last seen on January 18, 1937, at which time she had no complaints. Her erythrocyte count was 5 million, and hemoglobin was 109 per cent.

Case 7. Non-tropical sprue.

History: The patient, Mrs. J. V., aged 48, was seen on February 7, 1935, complaining of anemia, intermittent diarrhea of 32 years' duration, a burning sensation in the mouth and rectum, abdominal distress, flatulence, undernutrition, and insomnia. Upon examination undernutrition was noted. Face and neck were quite bronzed. The tongue was smooth. The abdomen was tympanitic. Some soreness and restriction of motion were noted in the left shoulder and hypertrophic changes were found in the terminal interphalangeal joints. The stools contained no parasites but were mushy and contained an excess of fat. The stomach contents were without free HCl after histamine stimulation. Blood calcium was 7 mg. and phosphorus 3.3 mg. per 100 c.c. of blood. Erythrocytes were 3.8 million, hemoglobin 83 per cent (Sahli). Volume index was 1.09. White blood cells 6,150. Differential count: Rod forms 10 per cent, segmented cells 37 per cent, eosinophiles 4 per cent, basophiles 0, lymphocytes 42 per cent, monocytes 6 per cent, juv. forms 1 per cent. Macrocytosis, anisocytosis, poikilocytosis, and polychromatophilia were present.

The patient was given a diet restricted in fat, dilute HCl, and 15 gm. of desiccated duodenal mucosa daily. On this regime she felt an improvement as early as the fourth day. On February 22, the fifteenth day of treatment, the erythrocytes were 4.9 million and the hemoglobin 85 per cent. The patient continued to do nicely for a period of three months. At the end of that time further effort to continue observations on the results of treatment were discontinued for the reason that the patient lived in a distant city and could not report.

Discussion of Cases

A critical analysis of the case histories presented indicates that the therapeutic effect of desiccated duodenal mucosa is similar to, or even better than, the results obtained from the use of desiccated stomach preparations. The dosage employed in the cases reported was in each instance much less

than the quantities recommended for the latter material yet the erythrocyte response amounted in all cases to 300,000 cells or more per week, whereas an increase of 100,000 cells per week is considered to be satisfactory with stomach preparations.

The reticulocyte response unfortunately could not be determined with sufficient frequency to absolutely establish the relative potency of the material employed and in no instance is there any assurance that the height of the reaction was recorded. In Case 1, however, an increase of 14.8 per cent occurred on the eighth day after administration of 15 gm. of desiccated duodenal extract. The initial erythrocyte count in this instance was 1.45 million. According to Bethell and Goldhamer's table for a similar initial count the height of the reticulocyte response after feeding 40 gm. of desiccated stomach mucosa daily should be 29 per cent. With less than half the dose, therefore half the expected increase of reticulocytes was obtained. In Case 4 with an initial count of 3.2 million the reticulocyte response at its height should be 3.1 per cent, after taking 40 gm. of stomach mucosa daily. In this case with 25 gm. of desiccated duodenal mucosa an increase to 5.9 per cent was found on the tenth day. The clinical improvement in every instance was satisfactory and normal erythrocyte levels were maintained in at least three cases for a sufficient time to exclude the possibility of spontaneous remission having occurred.

A study of six cases of gastrointestinal difficulty associated with anemia, diarrhea, and colitis has indicated that, in addition to its antianemic properties, the preparation has qualities which may be of considerable therapeutic value in the treatment of such conditions. The improvement noted may be due to the presence of intestinal ferments.

Comment

The above work it must be remembered deals with a material derived from the duodenal mucosa of swine. This cannot be considered in any way as direct proof that a similar antianemic substance may be found in the intestinal mucosa of man. A careful review of the literature, however, would indicate that such an assumption should be made. Castle's work with duodenal secretion should be carried further to show the effect on a primary anemia of the administration of human duodenal mucosa, or the response to the product of the interreaction between human duodenal mucosa and beef extract. It is possible that some chemical reaction or ferment activity may change or modify duodenal secretion so that in Castle's experiment negative results are obtained.

Conclusions

1. A study of the literature indicates a weakness in Castle's assumption that *intrinsic factor* is produced only in the stomach.

2. Many of the uncertainties arising from Castle's hypothesis may be

reasonably dispelled by the assumption that *intrinsic factor* is produced quantitatively in both the stomach and bowel.

3. Proof that potent antianemic material is found in the duodenal mucosa of swine is presented.

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THE ORIGIN OF PAROXYSMAL TACHYCARDIAS AS DETERMINED BY THE ESOPHAGEAL ELECTROGRAM *

By A. McGehee Harvey, M.D., *Baltimore, Maryland*

In order to differentiate clearly the various types of sudden increase in the cardiac rate electrocardiographic records are necessary. In view of the fundamental differences in the method of treatment employed in these instances of paroxysmal tachycardia an exact diagnosis is desirable. In many instances the auricular complexes are not clearly discernible in the three conventional leads, and the cardiac rhythm cannot be determined with certainty. For example, the difficulty in distinguishing paroxysmal auricular tachycardia and auricular flutter with one to one response is especially great.

The esophageal electrogram is of practical aid in the diagnosis of abnormalities of the auricular rhythm as the P-waves are large and clearly defined in these records. The method described by W. Hurst Brown [1] has been used in the study of the cardiac arrhythmias presented in this report. If care is taken to anesthetize thoroughly the pharynx with a 5 per cent solution of butyn no difficulty will be experienced in passing the electrode. In ambulatory patients the position of the esophageal electrode is checked by fluoroscopy. With the patient placed in the right anterior oblique position the cardiac outline is traced on a piece of tissue paper held in front of the fluoroscopic screen. The exact position of the electrode in relation to the posterior surface of the heart can be accurately recorded in terms of depth in centimeters from the teeth upon this outline. After this procedure has been carried out the electrode can be placed at the various points without fluoroscopic control. By averaging the results obtained by fluoroscopic control Brown found that the multiplication of the measurement in centimeters from the thyroid cartilage to the tip of the ensiform process by 1.33 always indicated the depth in centimeters from the teeth necessary to bring the electrode behind the left auricle. This method is used when fluoroscopy cannot be performed.

Three cases of paroxysmal supraventricular tachycardia, one case of paroxysmal ventricular tachycardia, and one of indeterminate origin have been studied in this manner. Before presenting them a brief description of the form of the normal esophageal record seems advisable.

When the esophageal electrode lies behind the left auricle the main characteristic of the P-wave is a sharp upstroke indicating electro-negativity of the small area just beneath the electrode. The onset of auricular activity is usually represented by a small upright or "extrinsic" deflection repre-

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From the Cardiographic Laboratory of the Department of Medicine, Johns Hopkins Hospital and University.

senting the summation of activation of points in the auricle distant from the electrode. The downward deflection just before the sharp upstroke or intrinsic wave indicates the rapid approach of the excitation wave to the cardiac muscle lying in closest approximation to the electrode. Whenever the electrode is not lying over the auricle the sharp upstroke or intrinsic deflection will be absent. Figure *7B* shows the form of the esophageal electrogram at various levels. There is no need to comment in detail on the form of the ventricular complexes in these records.

Paroxysmal Supraventricular Tachycardia

Case 1. M. B., a 63 year old white woman, had had an attack of palpitation followed by vertigo and loss of consciousness at the age of 18. She had had several similar attacks each year since that time, each sudden in onset and cessation, and varying in duration from several minutes to several days. She was first admitted to this hospital in 1924 when a diagnosis of auricular flutter was made. On two occasions the attacks were stopped by the use of quinidine. The cardiac rate was usually above 200 during the period of palpitation. Although several electrocardiograms were obtained while the fast rate was present, it was impossible to determine whether the fundamental rhythm was due to paroxysmal auricular tachycardia or paroxysmal auricular flutter with one to one response.

Five days before her admission in June 1936 while drinking iced water the patient noted the onset of palpitation and vertigo. During the next few days she grew progressively more dyspneic and was unable to sleep.

On admission the temperature was normal, the pulse rate 220 and the respiratory rate 30. Dyspnea and cyanosis were prominent, and the neck veins were engorged. There were arteriosclerotic changes in the retinal and peripheral vessels. Chronic bronchitis and emphysema were present, and many medium moist râles were heard at the lung bases. The heart was slightly enlarged. The sounds were of fair quality. The blood pressure was 100 mm. Hg systolic and 90 diastolic. The liver was enlarged, but no edema was present. A diagnosis of arteriosclerotic heart disease with congestive heart failure was made.

An esophageal electrode was passed without difficulty. The records obtained showed paroxysmal supraventricular tachycardia and not auricular flutter.

After 25 mg. of mecholyl the rhythm reverted to normal, a moderately severe attack of asthma ensued, and auriculo-ventricular nodal rhythm with inversion of the T-waves was present for a short while.

Interpretation of the Electrocardiograms. Figure 1. A. This is a record showing the three conventional leads. The rate is 75 and the P–R interval 0.13 sec. The QRS complexes are of low amplitude and thickened. Very small biphasic T-waves are present in each lead. *B.* The three conventional leads during an attack are presented here. The rhythm is regular at a rate of 230 per minute. It is difficult to be certain of the presence of any regularly spaced P-waves. *C.* and *D.* A simultaneous recording of Lead II and the esophageal electrogram (*C*) shows the sharp upstroke of the P-wave and the form of the ventricular complex. Record *D* taken during an attack shows several points of interest. Whereas in the normal esophageal record auricular activity was present for some time before the excitation wave passed beneath the electrode, the electrode was directly over the origin of the impulse during the tachycardia as the sharp upstroke or "intrinsic" wave is the first evidence of auricular activity. The P-wave falls on the upstroke of the T-wave soon after the termination of QRS complex. The P–R interval is longer than in the previous records. These findings suggest that an auriculo-ventricular nodal paroxysmal tachy-

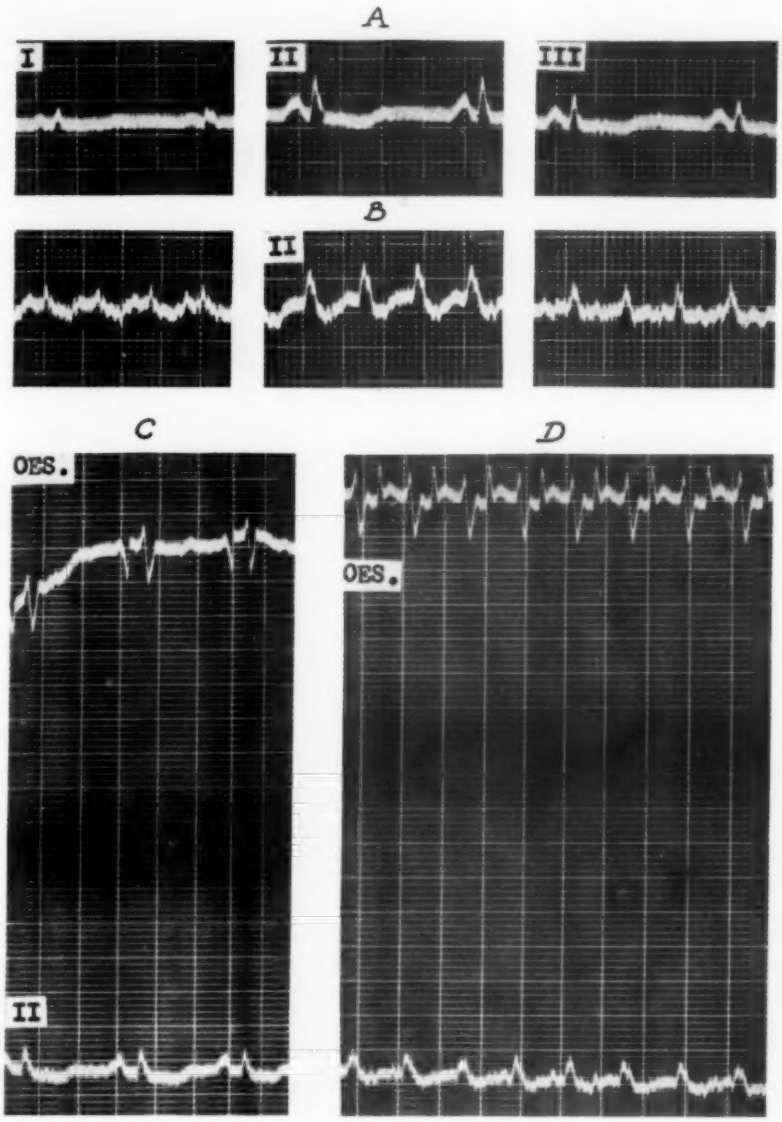

FIG. 1. Standardization 1 mv. = 5 mm. Heavy vertical lines in the curves mark the time in 0.2 sec. intervals.

cardia is present. One cannot be certain of this, however, as a delayed auriculoventricular conduction time is not infrequent in the presence of such a rapid cardiac rate. The form of the QRS complex is the same in each record. Particularly striking is the ease with which the P-waves are visualized in the esophageal curve of record *D* in contrast to the confusion encountered in the simultaneously recorded Lead II.

Figure 2. This unusual record shows the onset of an attack of tachycardia in this patient. The change in the form of the auricular complex with the onset of the fast rhythm is clearly visualized. Lead II is simultaneously recorded.

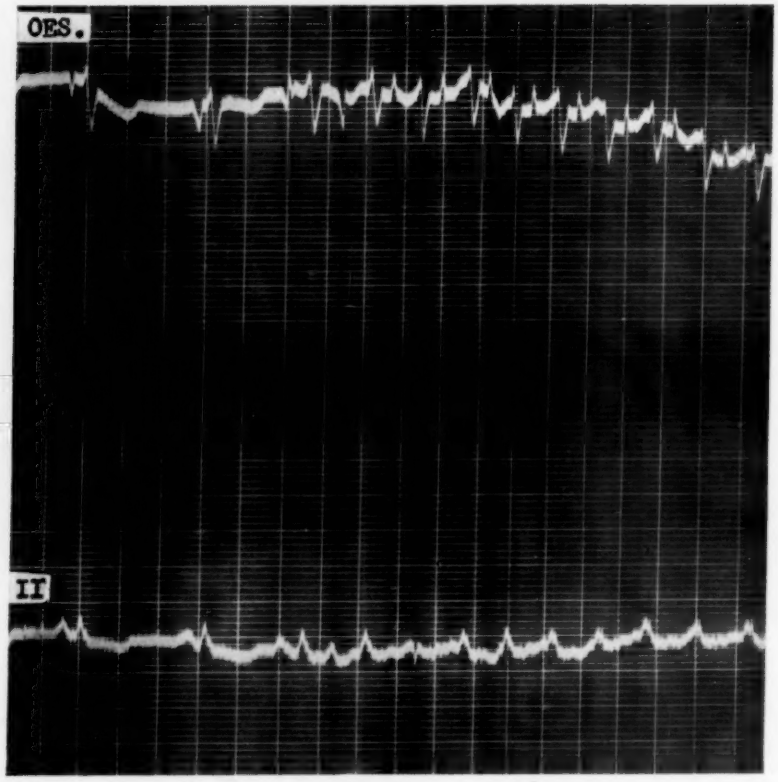

FIG. 2.

Case 2. Paroxysmal supraventricular tachycardia. L. B., a 37 year old white housewife, came to the Dispensary in February 1936, complaining of attacks of tachycardia. The attacks began eight years previously, shortly before her marriage. They increased in number during her first pregnancy, and have occurred from three to five times weekly since then. Sneezing, bending over, or any sudden effort usually was the precipitating factor. The tachycardia most often lasted only a few minutes, but occasionally persisted for two or three days. The attacks became more frequent and severe during the month prior to her visit. The past history was non-contributory.

The patient was a well developed and nourished, healthy-looking woman who felt perfectly well when the tachycardia was absent. The general physical examination showed nothing abnormal. The heart was not enlarged. The sounds were of good quality, no murmurs were audible, and the blood pressure was 110 mm. Hg systolic and 70 diastolic. A complete diagnostic survey revealed no foci of infection or any causative factor. There was no evidence of organic heart disease.

The patient was able to produce an attack by repeatedly bending over and touching her ankles; thus it was possible to make a complete study of the nature of the tachycardia. It was discovered that light pressure in the region of the right carotid sinus stopped the tachycardia immediately. The patient was taught to perform this simple maneuver. At a visit six months later she stated that no difficulty had been encountered in stopping each attack quickly in this manner.

The Electrocardiograms. Figure 3. B. This record was taken shortly after the cessation of an attack. The rate is 88, and the P–R interval 0.18 sec. The P-waves in Lead II are notched, and the T-waves are all of small amplitude. *A.* The electro-

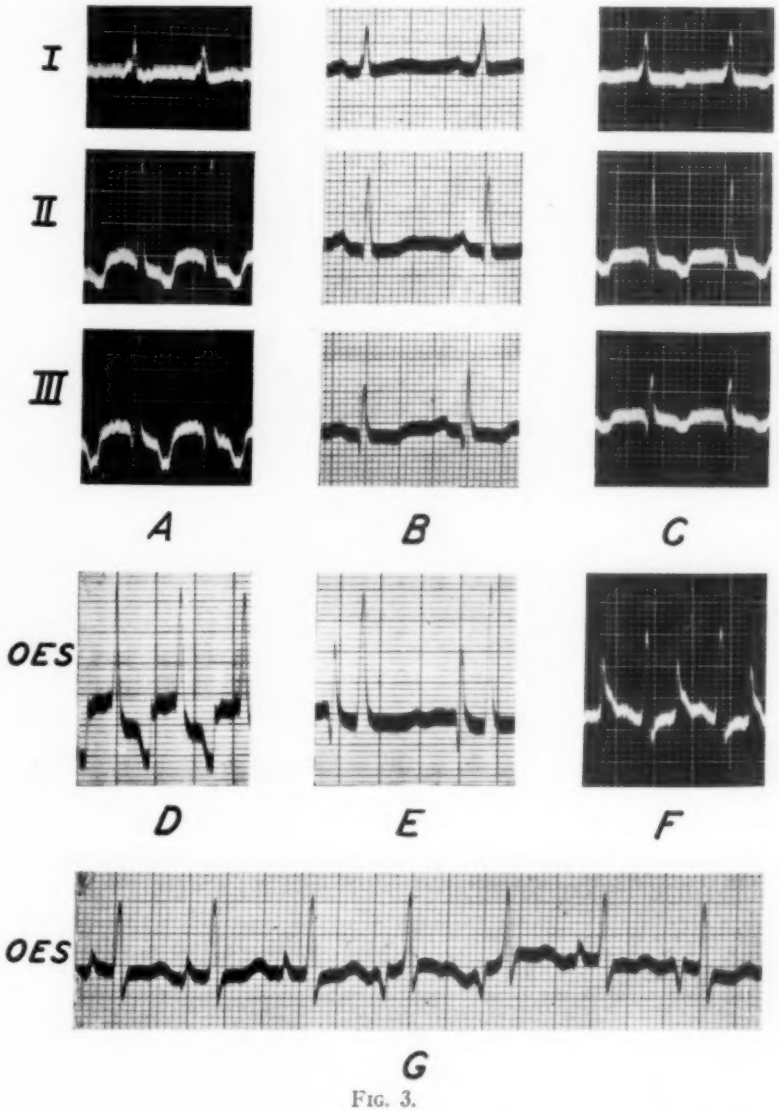

FIG. 3.

cardiogram during this attack reveals a rate of 150 which is quite regular. In Leads II and III the P-waves are superimposed on the end-deflection of the ventricular complex. The P–R interval is quite definitely longer than in the records taken at a normal rate. *C.* This record taken during a second paroxysm shows a P-wave of a different character. The rate is only 136, and the auriculo-ventricular conduction time is slightly longer. These differences suggest that the position of the ectopic focus varied in each of these attacks. *E.* In this normal esophageal record the P-waves are quite

distinct. *D* and *F* show the form of the esophageal lead in two separate attacks. In each the esophageal electrode was at the same level as in the normal record. In *F* the first evidence of auricular activity is a sharp upstroke while in record *D* changes due to activity at a point away from the electrode are visible before the intrinsic wave appears. *G*. This figure furnishes an explanation for the variable form of the records taken during periods of tachycardia. While this esophageal electrogram was being taken the patient held her breath and the position of the electrode remained the same.

The changes in the form of the auricular complexes in successive cycles are apparent. These variations are probably due to a shift in the pacemaker. Thus, in this patient there is more than one ectopic focus from which the paroxysms of tachycardia arise.

Figure 4. This attack was promptly stopped by pressure in the region of the right carotid sinus. The characteristic post-paroxysmal pause and the gradual return of the P–R interval to normal are illustrated. An extra-systole (P B) occurred during the pause. Lead II is not clearly recorded as the patient moved while the record was being taken.

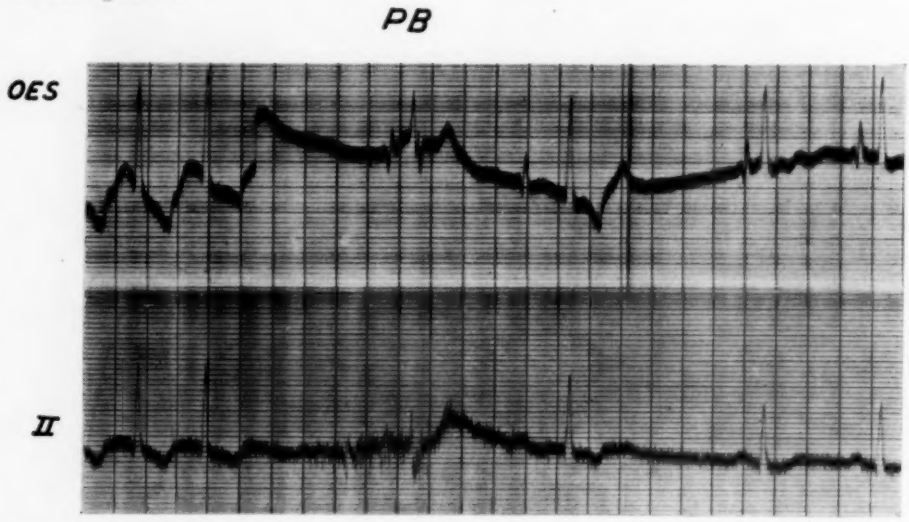

FIG. 4. The termination of an attack of paroxysmal tachycardia by carotid sinus pressure.

Case 3. Paroxysmal supraventricular tachycardia. F. W., a 49 year old white male clerk, had had attacks of paroxysmal tachycardia for a period of 29 years. From the ages of 8 to 12 he had several attacks of rheumatic polyarthritis. The attacks of tachycardia were of sudden onset and termination, lasting from a few minutes to several hours and occurring one to two times a week. They were increased in frequency and duration during periods of constipation and upper respiratory infection. On various occasions the attacks had been stopped by bending over, by a blow to the precordium, or by pressure on the eyeballs.

The patient was well developed and nourished. There were no evidences of cardiac insufficiency. The heart was slightly enlarged both to the right and left. The typical signs of mitral stenosis and aortic insufficiency were noted.

During an attack the rate suddenly increased to 187. The patient's only symptom was palpitation. After electrocardiographic records were obtained the attack was stopped by pressure on the eyeballs. Quinidine has been administered in prophylactic doses, and since that time the attacks have been both less frequent and shorter in duration.

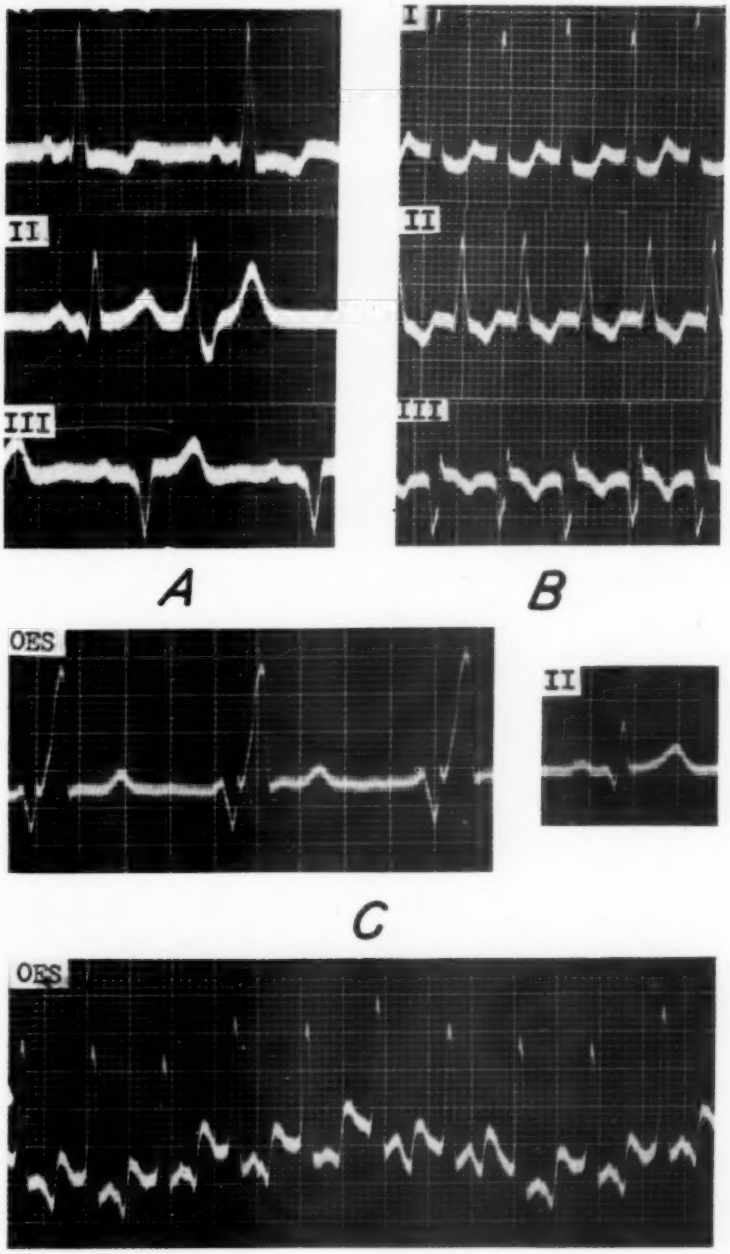

FIG. 5.

Electrocardiograms. Figure 5. A. The normal electrocardiogram shows a rate of 75 with a P–R interval of 0.19 sec. There is a left axis deviation. The QRS complex in Lead III is slurred. T_1 is biphasic, T_2 and T_3 upright. One ventricular extrasystole is present in Lead II. *B.* This record taken during a period of paroxysmal auricular tachycardia has a rate of 194. The P-waves and the T-waves are superimposed. The ventricular complexes are supraventricular in type. There is alternation in the amplitude of the QRS complexes. *C.* The normal esophageal lead shows a typical auricular complex composed of a small upright wave succeeded by a steep downward deflection as the excitation wave approaches the region in apposition to the electrode. Late in the complex the sharp upstroke or "intrinsic" wave appears. The duration of the intraventricular conduction time is 0.13 second in this record. The simultaneously recorded Lead II shows no such prolongation of the QRS duration. *D.* The esophageal electrogram during an attack shows clearly defined P-waves in contrast to the conventional leads. The rate here is only 176. The P–R interval is only 0.15 second as compared to 0.19 in the records with normal rhythm.

Case 4. Paroxysmal ventricular tachycardia. C. S., a 15 year old colored girl, came to the hospital on June 19, 1936, complaining of a sensation of choking and rapid heart action. She had always been healthy. There was no history of tonsillitis, rheumatic fever, or chorea. She stated that in August 1934, and again one year later she had had a similar illness lasting about 10 days. The present attack began one week before admission, and the patient had vomited several times each day.

The temperature was 100.6°, the pulse rate 220, and the respirations 38. The patient was well developed and nourished. She seemed uncomfortable but not acutely ill. The neck veins were a little full, and very rapid venous pulsations were visible. The heart was at the upper limit of normal in size. There was a diastolic shock in the second left interspace, and a prominent pulsation was visible there. The first sound was snapping in quality, and a triple rhythm was present at the apex. There was no evidence of cardiac insufficiency. The remainder of the physical examination was negative.

Following the administration of apomorphine the rate became normal, but the tachycardia reappeared within a few hours. The electrocardiogram revealed a tachycardia which was ventricular in origin. Mecholyl was tried but had no effect. About 24 hours after admission, after one gram of quinidine had been administered, the patient had a sudden stabbing pain over the precordium following which the heart rate became normal. After reversion a systolic apical murmur was audible, but diastole was clear. The roentgen-ray showed an accentuation of the second curve on the left. The position of the barium-filled esophagus was normal indicating that no pronounced enlargement of the left auricle was present. The diagnosis was paroxysmal ventricular tachycardia, with questionable rheumatic heart disease. The patient was discharged and advised to take a prophylactic dose of quinidine daily. No further attacks have occurred.

The Electrocardiograms. Figure 6. A. The record after reversion to normal sinus rhythm shows a rate of 107 with a P–R interval of 0.14 sec. The P-wave in the second lead is of comparatively large amplitude. The QRS complexes in Leads II and III are thickened. There is arching of the S–T intervals and all of the T-waves are inverted. In later records the left axis deviation disappeared, and the T-waves became upright. *B.* This record shows the ventricular tachycardia with a rate of 230. No P-waves are visible. *C* and *D.* These records show the esophageal electrograms, the first taken while normal sinus rhythm was present. The second taken during an attack shows the striking change which has taken place in the ventricular complexes. Again no auricular waves can be seen. The electrode was at the same level in each instance.

Case 5. Paroxysmal tachycardia of indeterminate origin. A 10 year old col-

ored girl came to the hospital on January 2, 1937, because of a rapid heart rate of two hours' duration. There was no history of rheumatic fever or chorea. During the first year of life the patient had had severe rhinopharyngitis complicated by otitis media and later acute tonsillitis with a membrane suggestive of diphtheria. Acute

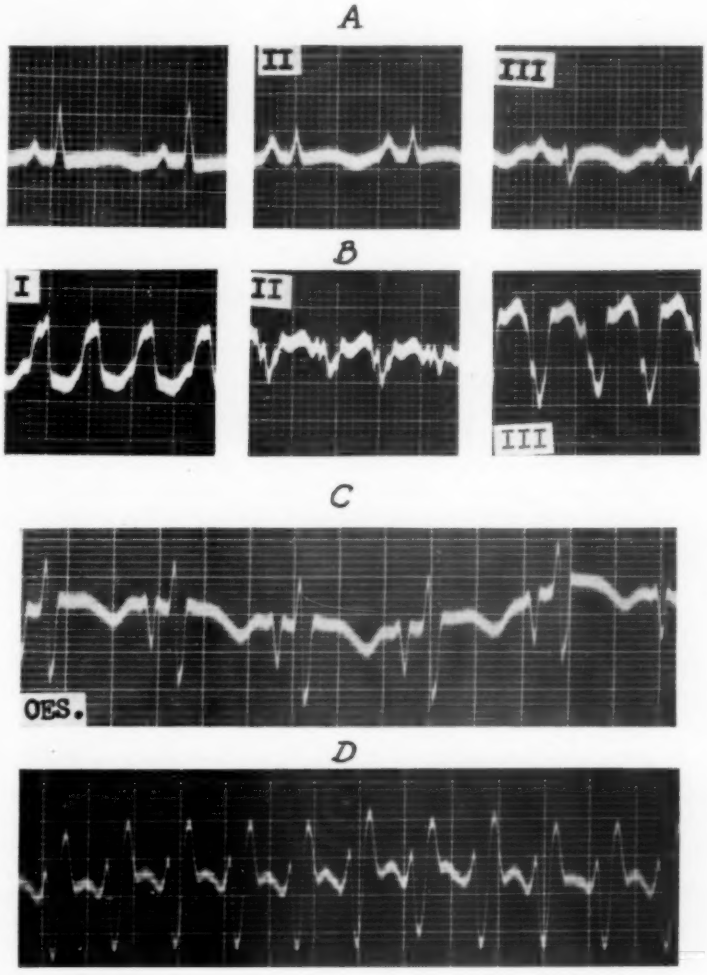

FIG. 6.

cervical adenitis developed one month later, which had to be drained. At five years of age she had measles and two months later laryngeal stridor which necessitated tracheotomy. Culture of the throat showed B. hemolytic streptococci but no diphtheria bacilli. An electrocardiogram taken at that time showed frequent ventricular extrasystoles. A tonsillectomy was done later, and the patient was well until April 1935, when she was admitted with lobar pneumonia. The heart was normal. The basal metabolic rate was not elevated.

In June 1936 she came to the hospital complaining of precordial pain. The pulse was so fast that it could not be counted. Before an electrocardiogram could be taken the cardiac rate had dropped to 94. An occasional ventricular extrasystole was present. Following this the patient was quite well until her present attack.

The temperature was normal. The eyes were a little prominent. The tonsils were cleanly removed. The lungs were clear. The heart was not enlarged. During the attack a rapid regular rhythm with a rate of 230 was present. The sounds were of good quality. The neck veins were engorged. The remainder of the examination was negative. When the cardiac rate had returned to normal, no murmurs could be heard.

After the electrocardiograms were taken efforts were made to stop the attack by vagal stimulation such as eye-ball pressure, carotid sinus pressure and finally mecholyl. All were unsuccessful. About five hours after the onset, after 0.3 gm. of quinidine sulphate had been given, the pulse rate was found to be 120. It was almost certainly a spontaneous reversion to normal rhythm.

The Electrocardiograms. Figure 7. A. This is the normal record with a rate of 91 and an auriculo-ventricular conduction time of 0.14 second. There is left axis deviation. The T-waves are upright. *B.* The normal esophageal electrograms taken at the levels indicated illustrate the sequence of changes in the auricular complex. *C.* and *D.* These records taken during the period of ventricular tachycardia contrast the ease with which the auricular complex is recognizable in the esophageal record in comparison to the conventional leads. The sharp upstroke is greatest with the electrode placed at 31 cm.

Without further evidence it is impossible to determine accurately whether this tachycardia was ventricular in origin with retrograde P-waves, or auricular with delayed intraventricular conduction. Only by means of a double esophageal electrode to determine the direction of spread of the auricular complex, an electrocardiographic record of the onset or termination of the attack, or by observation of the effect of rebreathing of oxygen on the form of the ventricular complex could further helpful information be obtained. The patient has had no further attacks during which these procedures could be carried out.

Discussion

The electrocardiographic records taken in these patients demonstrate the greater ease with which the auricular complex can be recognized during an attack of paroxysmal tachycardia by means of an esophageal lead.

Other methods of amplifying the auricular deflection so that its form could be determined in doubtful cases have been suggested. McGuire and Foulger [2] in 1931 described three cases in which they used a needle electrode inserted beneath the skin at the second and fifth right intercostal spaces near the sternum. By this means the P-waves were made more prominent, and the true nature of the arrhythmia could be determined.

Roth [3] employed a right pectoral chest lead to record tracings of auricular activity. The right arm electrode was placed on the right arm, and the principal or left arm electrode in the right pectoral region. A case of auricular fibrillation and one of mitral stenosis are recorded in which the auricular waves were more clearly visualized than in the conventional leads.

In two of the cases of supraventricular tachycardia included in the present report the auriculo-ventricular conduction time was longer than that recorded during normal sinus rhythm. Although delay in conduction in these cases is not frequent it does occur. It is sometimes difficult to determine definitely whether the abnormal pacemaker is situated in the auricle or whether an auriculo-ventricular nodal tachycardia is present.

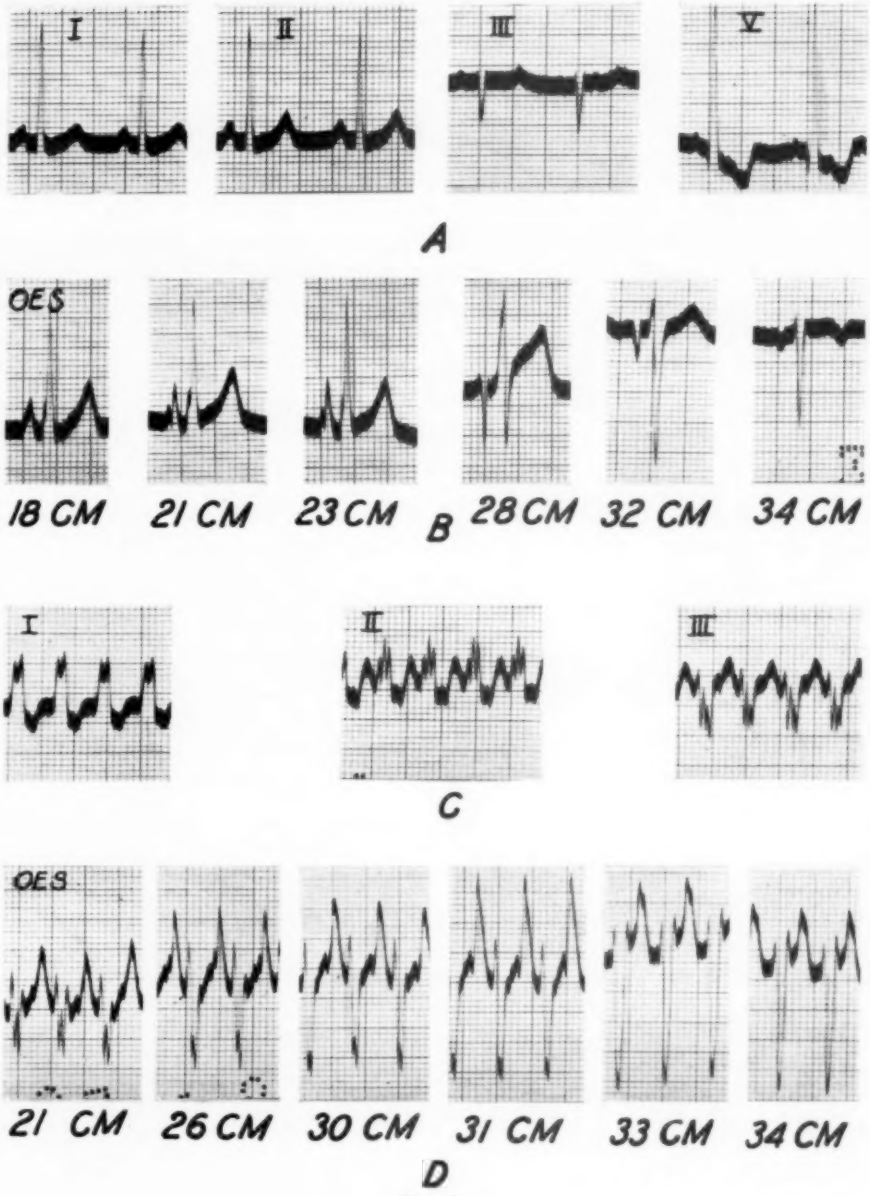

FIG. 7.

Case 2 is of interest because of the shift which occurred in the position of the auricular pacemaker. The form of the P-wave changed conspicuously, but there was only a slight variation in the P–R interval. White [4] published electrocardiograms illustrating a variation in the position of the pacemaker as shown by the shape of the P-wave, and the length of the P–R interval. In the same report he describes a case of paroxysmal tachycardia

arising in or very near the sino-auricular node which did not show an absolutely abrupt onset or offset. In case 2, of this series, although the onset and termination were prompt, there was a gradual acceleration of the rate to a maximum level followed by a gradual decline before the termination in some of the attacks. In this case the variation in the rate and the P–R interval in different attacks leads one to believe that there was more than one ectopic focus from which they arose.

In comparison with the incidence of paroxysmal supraventricular tachycardia, cases in which the ectopic focus is in the ventricle are uncommon. In contrast to the former group they are usually associated with organic heart disease, and in many instances occur after coronary thrombosis. The patient reported here was a young colored female in whom no definite organic heart disease could be discovered.

SUMMARY

The esophageal electrogram is helpful in detecting the auricular complexes when these are difficult to outline in the conventional leads.

Three cases of paroxysmal supraventricular tachycardia, one case of paroxysmal ventricular tachycardia, and one of indeterminate origin are presented. The appearance of the normal electrocardiogram and the esophageal electrogram is compared in each case.

Records are shown illustrating the onset and termination of paroxysmal auricular tachycardia. The esophageal lead and the conventional Lead II were recorded simultaneously.

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STUDIES ON EXPERIMENTAL HYPERTENSION

V. THE PATHOGENESIS OF EXPERIMENTAL HYPERTENSION DUE TO RENAL ISCHEMIA *

By HARRY GOLDBLATT, M.D., C.M., *Cleveland, Ohio*

THE production of persistent hypertension in dogs and monkeys has been reported in previous communications.[1-4] This was accomplished by constricting the main renal arteries by means of a special silver clamp devised for the purpose. In some of the dogs hypertension of severe degree has now existed for more than five years. The type of hypertension produced by this method depends upon the degree of constriction of the renal arteries. When the constriction is not very great, there is little or no disturbance of renal function accompanying the hypertension and it resembles benign hypertension in man. When the constriction is very severe, there is often accompanying damage of renal function which may also be severe. Such animals may die in uremia so that in this respect the hypertension resembles malignant hypertension in man. Constriction of splenic and of femoral vessels had no effect on blood pressure.[2] This is in keeping with the negative results obtained by Longcope and McClintock [5] from constriction of the superior mesenteric artery. These findings have been confirmed for the dog by other investigators.[6-18] The present report deals with experiments designed to determine the mechanism whereby the reduction of blood flow to the functioning components of the kidney, that is, renal ischemia, induces the development of hypertension.

That some pathological change in the kidney may be the cause of some forms of cardiovascular disease in man has been suspected on the basis of clinical observations and pathological findings from the time of Bright.[19, 20] That a pathological change in the kidney may initiate hypertension in man, especially the type that is associated with so-called diffuse vascular disease, has been recognized by some investigators for more than 50 years, since the existence of hypertension was first recognized. This view is still upheld by some, like Fahr,[21] who, on teleological grounds, regards the hypertension as compensatory to the reduced blood flow through the kidney, and by Volhard,[22a, 22b] on the basis of a humoral mechanism of renal origin, for at least the so-called malignant type of hypertension. It is opposed by others, like Kylin,[23, 24] who does not admit a primary renal origin even for the hypertension that accompanies glomerulonephritis. The mechanism whereby the kidneys produce their effect is still regarded as unsolved even by those who

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From the Institute of Pathology, Western Reserve University, Cleveland, Ohio.

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consider that these organs can play a primary part in the origin of hypertension.

Many experiments have been performed to determine whether the kidneys can be the primary site of origin of hypertension in animals.

A Summary of Other Experiments Designed to Determine the Possible Renal Origin of Hypertension

Bilateral nephrectomy.

Mosler,[25] (1912). Used rabbits. Insignificant elevation of blood pressure.

Backmann,[26] (1916). Used cats. No elevation of blood pressure.

Cash,[27] (1926). Used dogs. No elevation of blood pressure.

Hartwich,[28] (1930). Used dogs. No elevation of blood pressure.

Harrison, Blalock and Mason,[11] (1936). Used dogs. No elevation of blood pressure in 16 out of 18 dogs.

Reduction of the amount of functioning renal tissue.

Grawitz and Israel,[29] (1879). Used rabbits. Slight hypertrophy of heart, interpreted by the authors as due to hypertension.

Pässler and Heineke,[30] (1905). Used dogs. Slight elevation of blood pressure.

Backmann,[26] (1916). Used cats. Slight elevation of blood pressure.

Allen and collaborators,[31, 32, 33] (1923). Used dogs. Slight temporary elevation of blood pressure.

Mark,[41a, 41b] (1925, 1928). Used dogs. Slight elevation of blood pressure.

Anderson,[34] (1926). Used rabbits. No elevation of blood pressure.

Friedman and Wachsmuth,[35] (1930). Used dogs. No elevation of blood pressure.

Chanutin and Ferris,[36] (1932). Used rats. Great elevation of blood pressure.

Rytand, D. A. and Dock, W.,[37] (1935). Used rats. Great elevation of blood pressure.

Reduction of amount of renal substance by coagulation necrosis due to ligation of branches of renal arteries.

Janeway,[38, 39] (1908), assisted by Carrel.[40] Used dogs. Slight elevation of blood pressure.

Mark,[41b] (1928). Used dogs. No elevation of blood pressure.

Reduction of amount of renal substance by partial renal excision and unilateral nephrectomy combined with coagulation necrosis of part of the remaining kidney by ligation of branches of renal artery.

Cash,[42] (1924). Used dogs. Slight to moderate temporary elevation of blood pressure.

Mark and Giesendorfer,[43] (1930). Used dogs. Moderate temporary elevation of blood pressure.

Ferris and Heynes,[44] (1931). Used dogs. Slight temporary elevation of blood pressure.

Destruction of renal substance by irradiation of kidneys with roentgen-rays.

Hartman, Bolliger and Doub,[45] (1929). Used dogs. Moderate elevation of blood pressure.

Page,[6] (1935). Used dogs. Moderate elevation of blood pressure.

Renal infarction due to multiple emboli.

Senator,[46] (1911). Used cats. Injected liquid paraffin into renal arteries. No rise of blood pressure.

Cash,[42] (1924). Used dogs. Injected insoluble Berlin blue. No elevation of blood pressure.

Apfelbach and Jensen,[47] (1931). Used dogs. Injected particles of charcoal into renal arteries. No elevation of blood pressure.

Occlusion of one main renal artery or its branches.

Friedman and Wachsmuth,[35] (1930). Used dogs. Slight temporary elevation of blood pressure.

Occlusion of both main renal arteries.

Katzenstein,[48] (1905). Used rabbits and dogs. No rise of blood pressure.

Cash,[27] (1926). Used dogs. Moderate to severe elevation of blood pressure.

Occlusion (permanent or temporary) of renal arteries, veins and ureters.

Cash,[27] (1926). Permanent occlusion. Used dogs. No elevation of blood pressure.

Loesch,[49] (1933). Intermittent brief occlusion, every 2 or 3 days. Used dogs. Moderate persistent elevation of blood pressure.

Passive hyperemia (constriction of renal vein) of one kidney.

Pedersen,[50] (1927), and Bell and Pedersen,[51] (1930). Used dogs. Moderate temporary elevation of blood pressure.

Menendez,[52] (1933). Used dogs. Slight temporary elevation of blood pressure in some; none in others.

Compression of kidneys by oncometer.

Alwens,[53] (1909). Used cats. Acute experiments. Slight elevation of blood pressure.

Permanent obstruction of ureters.

Hartwich,[28] (1930). Used dogs. Moderate elevation of blood pressure.

Harrison, Mason, Resnik and Rainey,[54] (1936). Used dogs. Moderate elevation of blood pressure.

Temporary obstruction of one ureter followed by release of obstruction and excision of other kidney.

Rautenberg,[55] (1912). Used rabbits. Moderate elevation of blood pressure.

Effect of nephrotoxic substances.

Dominguez,[56] (1928). Used rabbits. Injected uranium salts. No elevation of blood pressure except in one animal that developed severe arterial and arteriolar sclerosis, especially in the kidneys.

Arnott and Kellar,[57, 58] (1935, 1936). Used rabbits. Injected sodium oxalate. Moderate elevation of blood pressure.

Scarff and McGeorge,[59] (1937). Used rabbits. Injected sodium oxalate. No elevation of blood pressure.

In the earlier investigations summarized above the hypertension that was observed was usually slight and lasted from only a few hours to several days. Some of the later investigators also reported the development of hypertension of slight or moderate degree and of short duration while others succeeded in producing moderate or severe hypertension of longer duration. Under practically every heading contradictory reports occur. These differences are partly due to the various methods, including cardiac hypertrophy, used for determining the existence of hypertension, the various types of animal employed and the slight changes of blood pressure which were regarded as significant by some and not by others. For some of the opposite results there is no obvious explanation. While the results of these experiments do indicate that various pathological changes in the kidneys can, in some way, play a primary part in initiating some degree of hypertension in animals, yet by none of these methods was a condition produced in the kidney which is comparable to that of the kidney in human hypertension that is associated with arteriolar disease. To reproduce a state resembling the condition of the kidney in arteriolar disease, any method must effect a decreased flow of blood to the functioning elements of this organ. Loesch [49] approximated this condition by completely occluding the circulation to and from the kidneys, and probably the ureter, for a short while, every two or three days, by clamping the entire pedicle of explanted kidneys. However, there is no good reason for believing that such intermittent occlusion of the arterial blood supply to the kidneys as well as complete interference with the return of venous blood from the kidneys reproduces the functional effects of arteriolar disease in the kidney. If the arteriolar disease of the kidney be responsible for the origin of hypertension then the more likely mechanism of its action is persistent reduction of blood flow to the functioning elements of this organ. The only method which would reproduce this exactly is one that would result in functional or organic narrowing of the arterioles of the kidney. No one has yet succeeded in producing either generalized arteriolar sclerosis or arteriolar sclerosis limited to the kidneys. The closest approach, therefore, to the functional effects of arteriolar dis-

ease on the kidneys has been accomplished by reducing the calibre of the main renal arteries alone,[1-4] with resultant renal ischemia, due to persistent reduction of blood flow into the organs. It was considered possible, therefore, that an elucidation of the mechanism of development of this type of experimental hypertension might make some contribution to our knowledge of the pathogenesis of the hypertension in man that is associated with arteriolar sclerosis and consequent ischemia of the kidneys. This is to be regarded as a preliminary communication on this part of the subject.

Experiments

The following experiments were performed for the purpose of elucidating the mechanism of hypertension due to renal ischemia.

Release or Removal of the Clamp. In six dogs, one or both clamps were released or removed some time after hypertension due to renal ischemia had

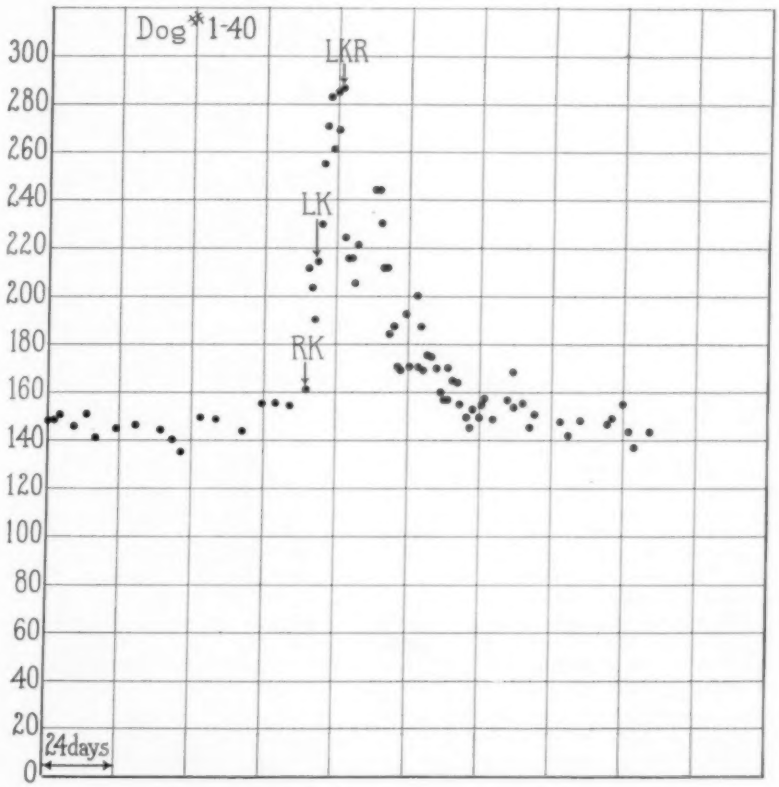

Figure 1. Dog 1–40. Female. 13.4 Kg.

● = Systolic blood pressure, van Leersum carotid loop method. RK = Right main renal artery severely constricted. LK = Left main renal artery severely constricted. LKR = Left clamp completely released but left on the artery.

The blood pressure, which had risen to a very high level after the constriction of the second renal artery, fell to normal in about one month after the release of the clamp on this artery.

been established. Quite promptly, but after a variable period, the blood pressure in these animals returned to the original level. In Dog 1–40 (figure 1), release of one clamp was followed by a rather slow fall of the blood pressure to the original level. In this animal there was no impairment of renal function. In Dog 2–67 (figure 2), after unilateral nephrectomy (LN), severe constriction of the main artery of the remaining kidney (RK_1) resulted in severe hypertension and severe impairment of renal function. When the clamp was released, (RKR_1) blood pressure and renal function promptly returned to normal. Reconstriction of the artery (RK_2) again resulted in hypertension and uremia. Slight release of the constriction (RKR_2) relieved the uremia but the blood pressure remained slightly elevated.

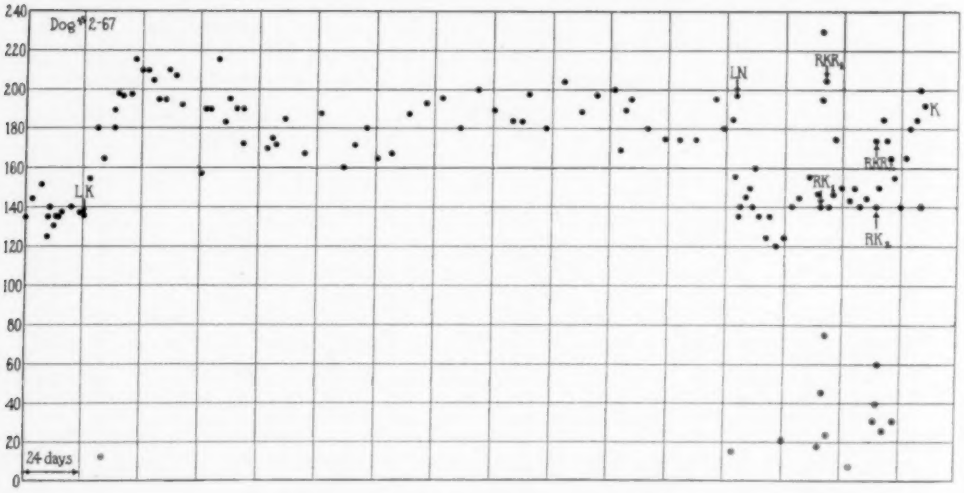

FIGURE 2. Dog 2–67. Female. 13.6 Kg.

● = Mean blood pressure, mm. Hg; ⊙ = blood urea mg. per 100 c.c. plasma. LK = Left main renal artery severely constricted. The blood pressure became greatly elevated. During about ten months after this the blood pressure remained elevated but gradually fell to a moderately elevated level. LN = The ischemic left kidney was excised and the blood pressure promptly fell to the normal level. RK_1 = The right main renal artery was severely constricted. The blood pressure became elevated and uremia developed. RKR_1 = The clamp on the right main renal artery was released. The blood pressure, blood urea, creatinine and non-protein nitrogen promptly returned to normal. RK_2 = The right main renal artery again constricted. Elevated blood pressure and uremia again resulted. RKR_2 = The right main renal artery partly released. Blood pressure dropped temporarily, then rose again and remained elevated. The animal developed severe uremia. K = Killed.

Removal of the Ischemic Kidney During the Period of Hypertension Following the Constriction of One Main Renal Artery. It was shown in the original communications [1, 2] that hypertension of some degree follows the constriction of the main renal artery of only one kidney but that after a variable period the blood pressure tends to return to the original level. In some dogs the blood pressure remains elevated for a considerable period following unilateral renal ischemia. In one dog, 2–67 (figure 2), the mean

blood pressure remained at a higher level than normal for about nine months following the constriction of the main renal artery of only one kidney. During this period there was no impairment of renal function. After the removal of this kidney (LN) the blood pressure promptly fell to the normal level. Severe constriction of the main renal artery of the remaining kidney

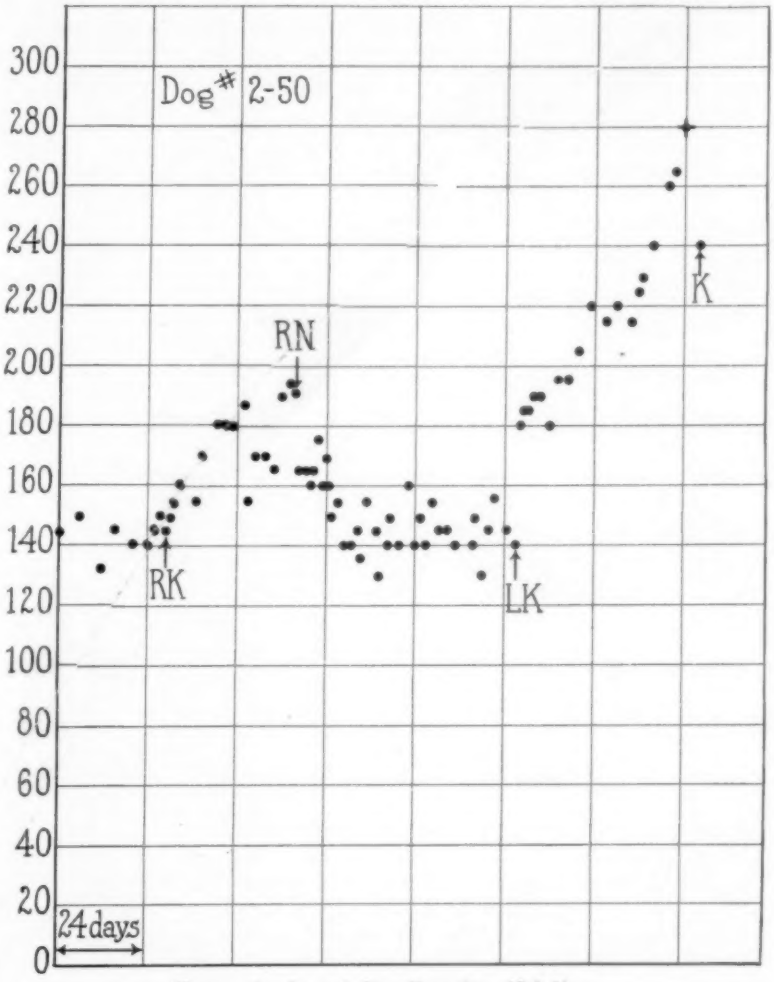

FIGURE 3. Dog 2–50. Female. 17.8 Kg.

● = Mean blood pressure, mm. Hg. RK = Right main renal artery moderately constricted. RN = Right nephrectomy at a time when the mean blood pressure was elevated resulted in its prompt return to normal. LK = Severe constriction of main renal artery of left kidney. This was followed by very high elevation of mean blood pressure. + = The mean blood pressure at this time was more than 300 mm. Hg. K = Killed.

(RK_1) resulted in reëlevation of mean blood pressure and impairment of renal function. In two other dogs also, at the height of elevation of blood pressure, after moderate to severe constriction of the main renal artery of one kidney, this ischemic kidney was excised. Dog 2–50 (figure 3), illus-

trates what happened in these animals. As in the case of Dog 2–67 (figure 2), removal of the ischemic kidney (RN) was followed by a prompt return of the mean blood pressure to the original level. Constriction of the main renal artery of the remaining kidney (LK) was followed by a prompt re-elevation of blood pressure which persisted. The results of these experiments indicate the importance of ischemia as the pathologic change and the kidney as the primary site of origin of this type of hypertension.

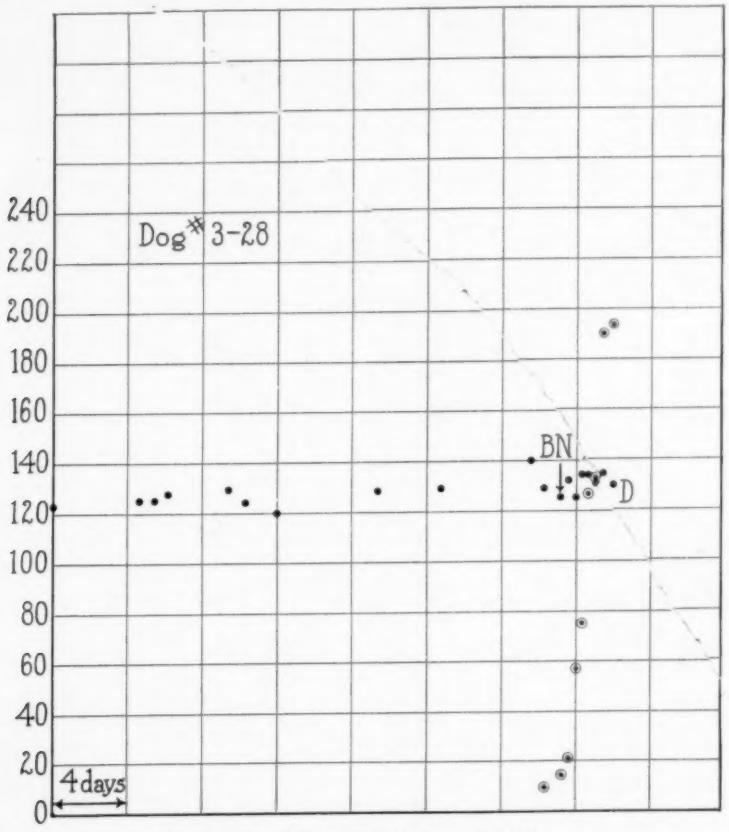

FIGURE 4. Dog 3–28. Male. 16.6 Kg.
● = Mean blood pressure, mm. Hg. ⊙ = Blood urea nitrogen mg. per 100 c.c. plasma. BN = Bilateral nephrectomy. The blood pressure did not become elevated. D = Died.

Bilateral Nephrectomy. If uremia alone were the cause of hypertension, then the removal of both kidneys, which is always followed by the development of uremia, should also, invariably, be followed by the development of hypertension.

In five dogs, both kidneys were removed. In three, bilateral nephrectomy was performed at one time and in two, the nephrectomies were separated by an interval of a week or longer. Most of the animals appeared in good condition for about 48 hours following the operation. All the animals died

in uremia but the blood pressure did not rise during the period of survival which varied from two to five days. Figure 4, Dog 3–28, illustrates one of these experiments. This finding is in keeping with the results obtained by other investigators.[11, 25, 26, 27, 28]

Occlusion of the Main Renal Artery of Both Kidneys. It might be considered that occlusion of both main renal arteries would be equal to, and give the same results, as bilateral nephrectomy. This is not the case. In

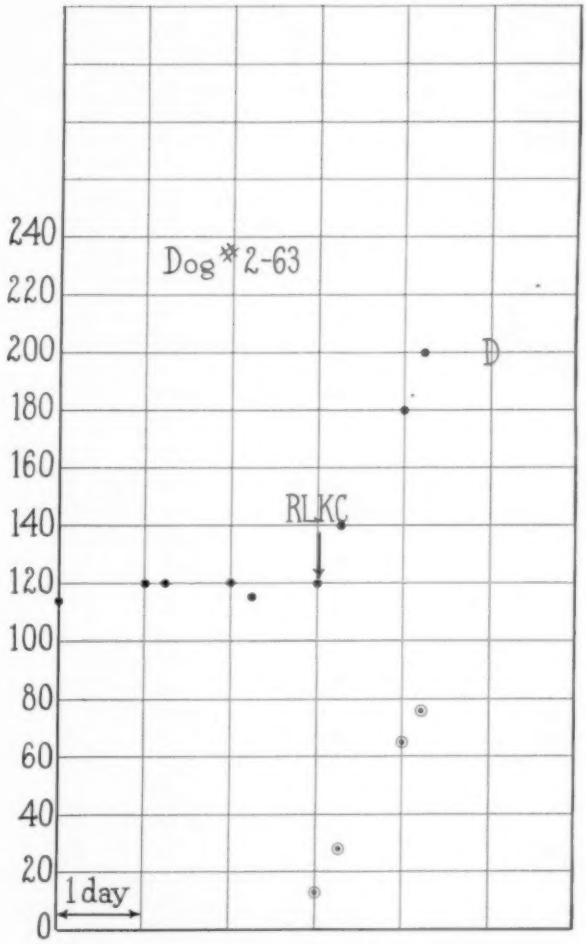

FIGURE 5. Dog 2-63. Female. 16.2 Kg.
● = Mean blood pressure, mm. Hg. ⊙ = Blood urea, mg. per 100 c.c. of plasma. RLKC = Both main renal arteries occluded. The blood pressure rose to quite a high level. D = The animal died in uremia.

four dogs the main renal artery of both kidneys was clamped completely at one operation and in two dogs the occlusion of the second artery was carried out after an interval of a week or longer. The complete occlusion of one

main renal artery was not followed by either uremia or a significant elevation of blood pressure. In all four animals, however, simultaneous occlusion of the main renal artery of both kidneys was followed by the development of severe uremia and slight or moderate elevation of the blood pressure. The degree of hypertension in the animals with both renal arteries occluded was not as great as in dogs with both main renal arteries only moderately or

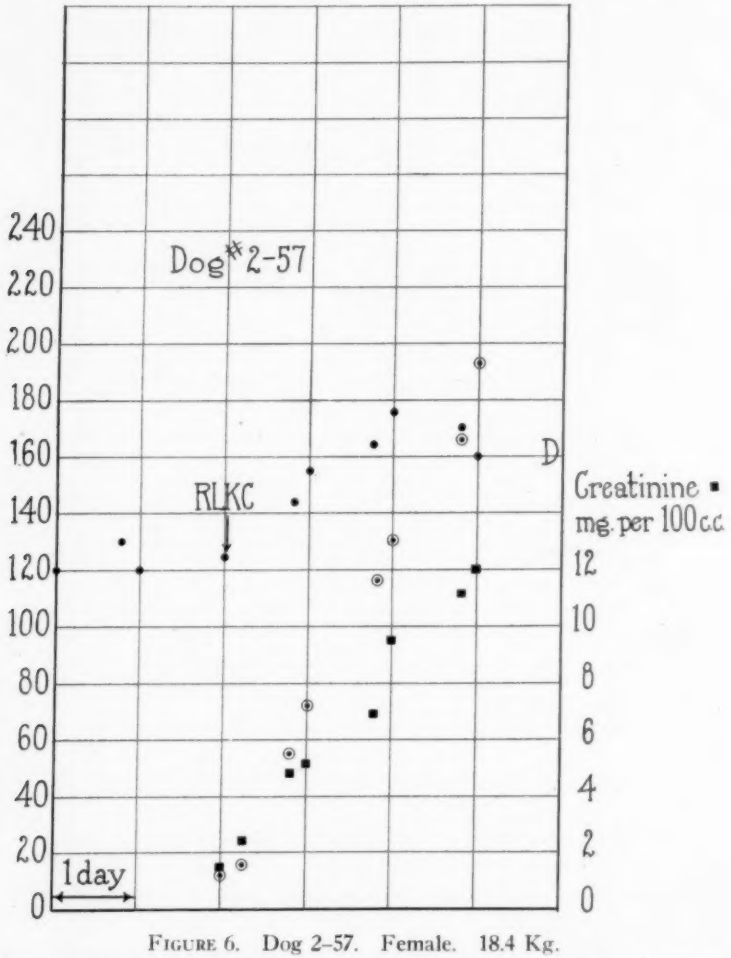

FIGURE 6. Dog 2–57. Female. 18.4 Kg.

● = Mean blood pressure, mm. Hg. ⊙ = Blood urea, mg. per 100 c.c. of plasma. ■ = Blood creatinine mg. per 100 c.c. of plasma. RLKC = Right and left main renal arteries occluded. The blood pressure showed a moderate elevation following the occlusion of the arteries. D = The animal died in uremia.

severely constricted.[2] The period of survival was about the same as that of the bilaterally nephrectomized animals. In the animals with both main renal arteries occluded, as in those bilaterally nephrectomized, the shock of the operation was evidently not great and for about 48 hours they seemed in

excellent condition. Both groups survived about the same period and all developed severe uremia, yet the animals with both arteries occluded did show a significant elevation of blood pressure which is illustrated for three of the dogs in figures 5, 6 and 7, while the nephrectomized animals failed to show a rise of blood pressure. In Dog 2–65, as a control, all of the arteries to the spleen were tied off completely (figure 7), some time before

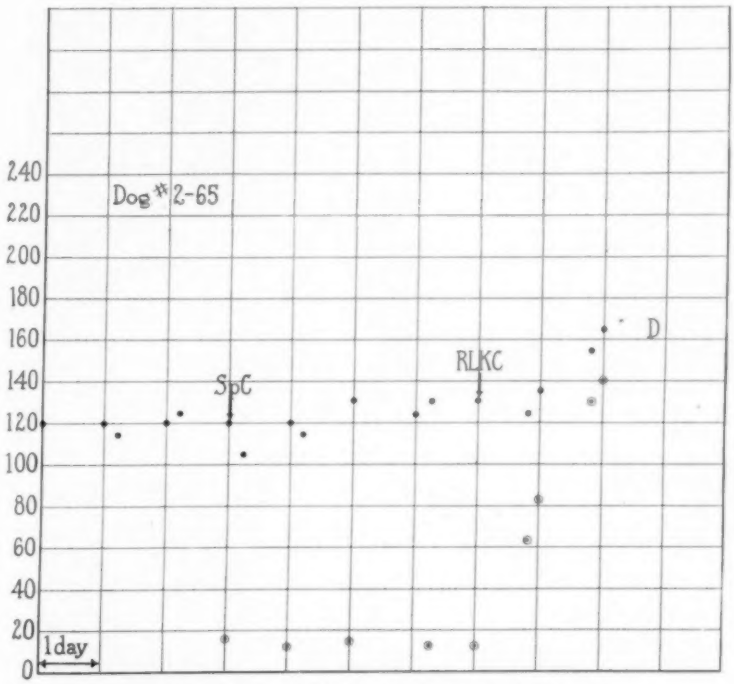

FIGURE 7. Dog 2-65. Female. 15.2 Kg.

● = Mean blood pressure, mm. Hg. ⊙ = Blood urea nitrogen mg. per 100 c.c. of plasma. SpC = Splenic arteries occluded. There was no significant rise of blood pressure after this procedure. RLKC = Right and left main renal arteries occluded. After this there was a moderate elevation of blood pressure. D = The animal died in uremia.

the renal arteries were occluded. The occlusion of the splenic vessels was not followed by a significant elevation of mean blood pressure. When both main renal arteries were occluded (RLKC) (figure 7), the blood pressure became slightly elevated, severe uremia developed and the animal died.

That a dog can survive for a long time the occlusion of both main renal arteries, provided the occlusion is not accomplished abruptly, has been well shown by four animals, in which the occlusion was accomplished in two or more stages. One dog has proved this very strikingly. At the second clamping of both main renal arteries, carried out successively about one year after the initial partial constriction, both main renal arteries were occluded. This animal survived the complete occlusion of both main renal arteries for four years. Hypertension of severe degree persisted during the entire

period and renal function, as shown by urea clearance, was only slightly affected. At autopsy, one kidney was very small and the other only moderately reduced in size. No accessory arteries were found except those that entered the kidney through the capsule. Other experiments of this kind, to be reported later, are being carried out to determine the exact source and extent of the supply of blood to such kidneys.

Discussion

As in the case of partial constriction of both main renal arteries,[2] the hypertension which follows occlusion of both main renal arteries can be explained by a possible nervous reflex from the kidney by way of the central nervous system to the peripheral vasomotor apparatus or by some humoral mechanism, or by a combination of both mechanisms.

That hypertension due to occlusion of both renal arteries is not due to a nervous reflex from the kidney is indicated by the fact that in some of these animals the renal pedicle was carefully denervated before the clamp was applied. It has also been shown by other investigators,[6, 10] and we have confirmed this, that renal denervation does not interfere with the development of experimental hypertension due to partial constriction of the main renal arteries. Section of the splanchnic nerves in the thorax, combined with excision of the lower four thoracic sympathetic ganglia, does not interfere with the development of hypertension or permanently reduce the hypertension produced by renal ischemia.[3] In an investigation soon to be published in collaboration with Dr. W. B. Wartman, it will be shown that section of the anterior nerve roots, from the sixth dorsal to the second lumbar inclusive, also does not interfere with the development of hypertension or permanently reduce the hypertension produced by renal ischemia. Finally, Freeman and Page [60] have shown that total sympathectomy does not interfere with the development of hypertension due to bilateral renal ischemia. These results are not to be interpreted as evidence or proof that the surgical procedures being practised on human beings with hypertension are not justifiable and that no improvement is to be expected from these procedures. What they do show is that in experimental hypertension, due to the permanent renal ischemia effected by the clamps, section or excision of various portions of the nervous system controlling a large part of the vasomotor mechanism of the abdominal organs, does not result in prevention or reduction of this type of experimental hypertension. These experiments serve to emphasize the importance of the reduction of the circulation to the functioning components of the kidney rather than a primary effect on the general vasomotor mechanism of the abdomen as the cause of this type of hypertension. This is in keeping with the views of Prinzmetal and Wilson [61] and of Pickering [62] about the secondary part played by the vasomotor mechanism in human hypertension. In man it is at least possible that as a result of some or all of the surgical procedures being practised on the

nervous system for the cure of hypertension, actual improvement of the circulation to the functioning components of the kidney may occur. Dilatation of renal arterioles without fixed organic changes in their walls might occur in some cases, as a result of these procedures. Since, in man, there is frequently no narrowing of the large renal vessels to interfere with the flow of blood into the kidney, it is at least conceivable that improved circulation to the functioning components of the kidney may follow as a result of dilatation of arterioles. This improvement of renal circulation could then account for the fall of blood pressure which has been observed in about the same rather small percentage of cases treated by the various surgical procedures on the nervous system. This view is in agreement with that of Peet [69] on the mode of action of resection of the splanchnic nerves in lowering the blood pressure in human beings with hypertension. It is not, however, the view that is generally accepted by those who have been performing operations on the nervous system for the cure of hypertension in man.[63-75] They prefer to regard the improvement following section or excision of the nerves as due to the elimination of their control over the corresponding portion of the vasomotor mechanism. The same improvement of the circulation cannot happen, or can happen to only a very limited degree, as the result of increased dilatation of the arterioles in the experimental kidney, as long as the main renal artery remains constricted by the clamp. These observations do minimize the importance of the effect of the vasoconstrictor mechanism in the abdomen in hypertension due to renal ischemia, because the removal of this mechanism by the various surgical procedures does not prevent or cure the hypertension as long as the clamps remain applied and the blood flow to the functioning components of the kidneys remains unimproved.

If the mechanism whereby constriction of the main renal arteries produces its effect on blood pressure be humoral and of renal origin then, in the case of the hypertension which also follows occlusion of both main renal arteries, it must be assumed that the natural accessory circulation through the capsule which may become more prominent in these circumstances, is sufficient to wash some hypothetical " effective substance " into the systemic circulation through the main renal veins. The term " effective substance " will be used in this paper to avoid commitment to the existence of a direct pressor substance rather than one which acts indirectly to produce the pressor effect. The effective substance, for example, might act synergistically with a known pressor hormone from an endocrine organ, such as the hypophysis or adrenal. It is also possible for the hypothetical effective substance from the kidney to act by sensitizing the contractile elements of the arterioles to the action of the pressor hormone, or the reverse may be the case. The effective substance might also produce its effect by neutralizing or reducing the amount of a hypothetical depressor substance circulating in the blood. That there may be an effective substance from the kidney is indicated by

reports of the pressor effect of extract of ischemic kidneys from dogs with experimental hypertension,[11, 15, 17] and of arteriosclerotic kidneys [13] from human beings with hypertension. However, the results of such investigations should be interpreted with caution because a pressor effect has also been obtained with extracts of normal kidneys [118, 119] and with extracts of various

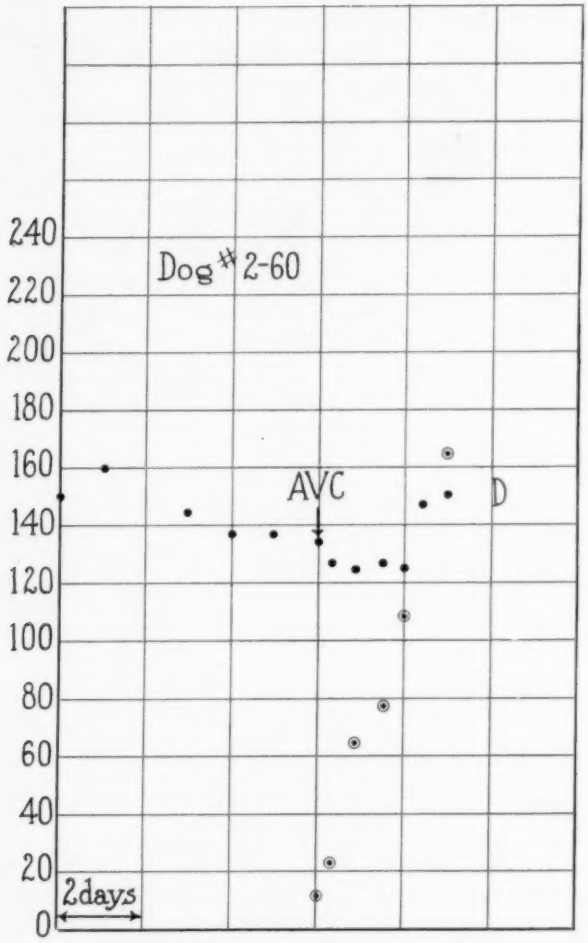

FIGURE 8. Dog 2–60. Male. 16.6 Kg.

● = Mean blood pressure mm. Hg. ⊙ = Blood urea nitrogen mg. 100 c.c. plasma. AVC = Both main renal arteries and veins occluded. The blood pressure did not become elevated. D = Died.

other normal organs.[120] The existence of a pressor substance in the systemic or renal vein blood of animals with hypertension due to renal ischemia has not been demonstrated [12] and no greater quantity of pressor substance than the normal has been found [12] in the extract of plasma of dogs with this type of experimental hypertension. It has not been proved that the systemic

blood, spinal fluid, or urine of human beings with hypertension of any type invariably contains a pressor substance. Many reports of the finding of a pressor substance [76-104] and of the failure to find a pressor substance [105-117] have been published. A discussion of these results would serve no useful purpose here. The pitfalls of such investigations were well shown by O'Connor.[126] The burden of the proof still rests with those who claim the

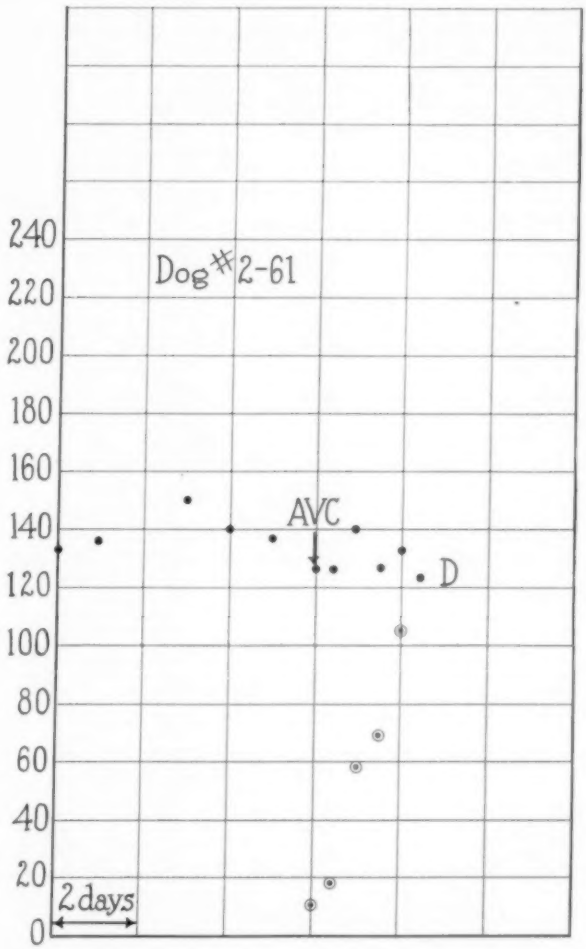

FIGURE 9. Dog 2-61. Female. 14.8 Kg.

● = Mean blood pressure mm. Hg. ⊙ = Blood urea nitrogen mg. per 100 c.c. plasma. AVC = Both main renal arteries and veins occluded. The blood pressure did not become elevated. D = Died.

invariable presence of an unusual amount of a known pressor hormone or of a new kind of pressor substance in pure or extracted blood, spinal fluid or urine of human beings with hypertension, especially the so-called benign or essential type. The experiments which follow are part of an investigation

that is being carried out to determine the part played by a possible humoral mechanism in the pathogenesis of hypertension due to renal ischemia.

Constriction or Occlusion of Both Main Renal Arteries with Simultaneous Occlusion of Both Main Renal Veins. One obvious but indirect way of testing for a possible humoral mechanism originating in the kidney is to constrict or occlude the main renal arteries, procedures which are now known to produce hypertension, and, at the same time, to occlude the main

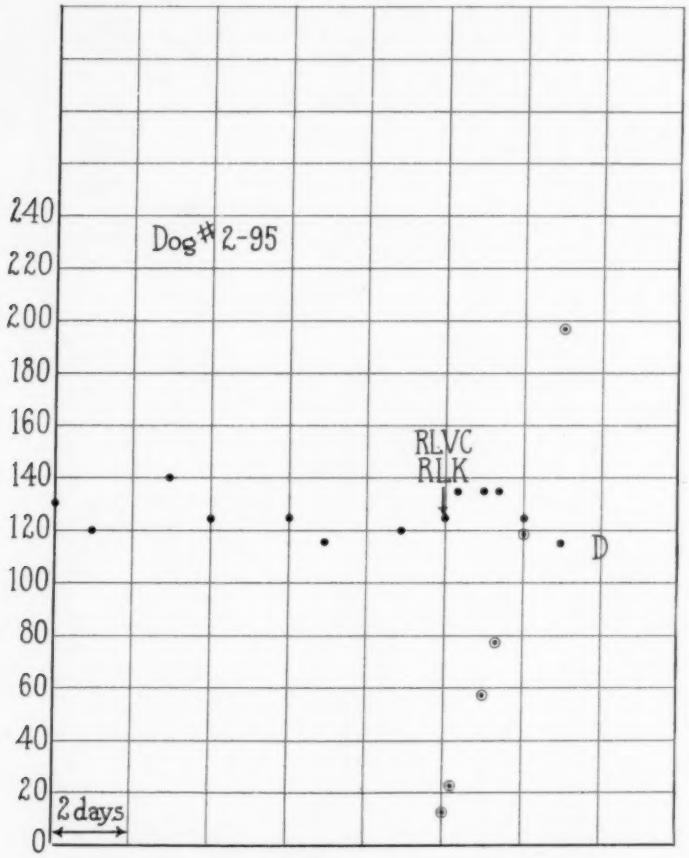

FIGURE 10. Dog 2-95. Female. 16.4 Kg.
● = Mean blood pressure, mm. Hg. ⊙ = Blood urea nitrogen mg. per 100 c.c. RLVC = Both main renal veins occluded. RLK = Both main renal arteries severely constricted. The animal died in uremia but the blood pressure did not become significantly elevated.

renal veins in order to prevent the hypothetical effective substance from leaving the kidneys. Failure of development of hypertension would be evidence in favor of a humoral mechanism originating in the kidney as the cause of the hypertension.

In two dogs (2–60 and 2–61) the main renal arteries and veins of both kidneys were occluded at one time. The blood pressure and some of the

chemical changes in the blood of these dogs are illustrated in figures 8 and 9. Both developed severe uremia but no rise of blood pressure occurred during the short period of survival. These results are in keeping with those of Cash [27] who found that no elevation of blood pressure occurred in dogs after the permanent occlusion of both main renal arteries, veins and ureters.

In two dogs (2–51 and 2–95) the main renal veins were occluded and the main renal arteries were only severely constricted. The animals developed severe uremia but no elevation of blood pressure occurred during the short period of survival. Figure 10 illustrates the blood pressure and chemical changes in the blood of one of these animals, Dog 2–95.

Since it has been shown that the permanent constriction or occlusion of the main renal arteries alone is followed by a definite rise of blood pressure, these results may be interpreted as indicating the probable interference with the entrance of the hypothetical effective substance into the systemic circulation by way of the renal veins.

The Part Played by Endocrine Organs in the Origin of Hypertension Due to Renal Ischemia

As part of the study of the humoral mechanism, an attempt has been made to investigate the part played by the endocrine organs that are known to produce a vaso-pressor hormone.

Hypophysis. Page [7] has shown that in dogs, hypophysectomy does not prevent the development of experimental hypertension due to renal ischemia, but that it does reduce the blood pressure in some animals with this type of hypertension. The significance of these contradictory findings cannot be evaluated at the present time. More experiments of this kind should be performed. The effect on this type of hypertension of removal of the various portions of the pituitary body have not yet been investigated.

Adrenals. In a previous communication [2] an experiment on Dog No. 8–9 was described in which excision of the right adrenal, the destruction of the medulla of the left adrenal, denervation of this adrenal and section of the left splanchnic nerves in the abdomen did not prevent the development of hypertension after the renal arteries were moderately constricted. The only conclusion that can be drawn from this experiment is that hypertension can develop in the absence of the medulla of both adrenal glands, as a consequence of renal ischemia, and that the presence of the medulla of the adrenal is not necessary for the development of this type of hypertension. Since then other experiments have been performed which were designed to determine the part which the cortex of the adrenal gland may play in the development of experimental hypertension due to renal ischemia. This is in the nature of a preliminary communication on this subject. The study is being continued and full details, including chemical studies, will be published later in collaboration with Dr. R. F. Hanzal. Up to the present time the following experiments have been performed.

Bilateral Adrenalectomy, without Supportive or Substitution Therapy, and Renal Ischemia. In this group of animals no supportive (sodium chloride and sodium bicarbonate or sodium citrate by mouth) or substitution (intra-venous cortical extract *) therapy was given after the removal of both adrenals.

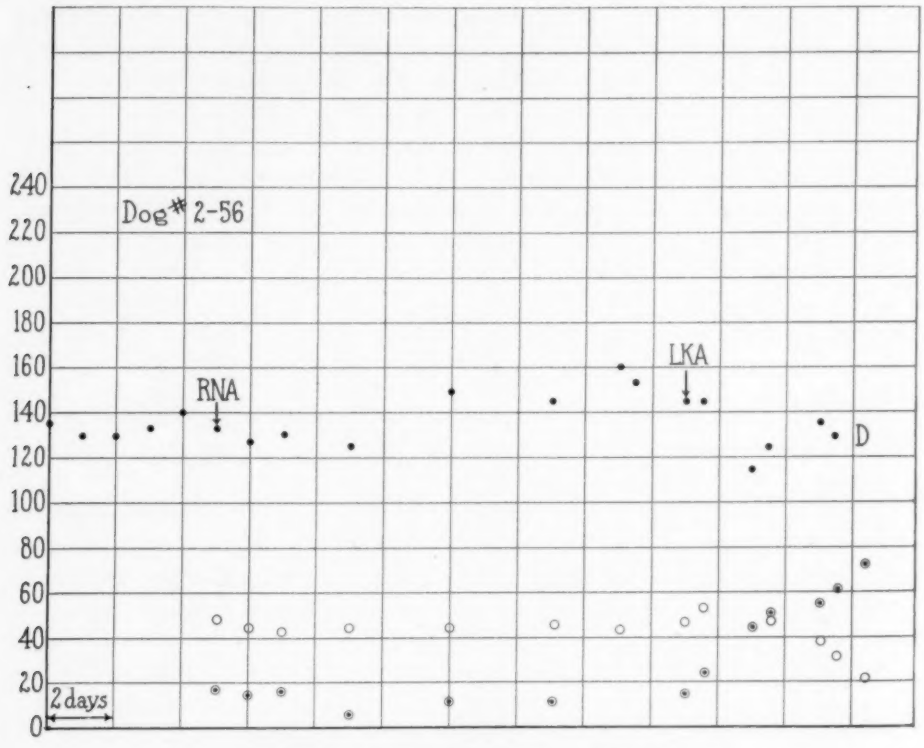

FIGURE 11. Dog 2–56. Female. 23.2 Kg.

● = Mean blood pressure, mm. Hg. ⊙ = Blood urea nitrogen mg. per 100 c.c. of plasma. ○ = CO_2 combining power, volumes per 100 c.c. RNA = Right adrenalectomy and right nephrectomy. If anything, a slight elevation of blood pressure occurred after these procedures. LKA = Left adrenalectomy and left main renal artery severely constricted. The animal developed uremia and the blood pressure fell. D = The animal died in uremia.

In three dogs, both main renal arteries were permanently constricted at the time of the second adrenalectomy. In two of these (2–56 and 2–62) the first adrenalectomy preceded the second by about two weeks, but in one animal the adrenalectomy and the constriction of both main renal arteries were carried out at the same time (Dog 3–22). The blood pressure did not become elevated in any of these animals, but the period of survival was short. (Figure 11.)

* The cortical extract used in these experiments was Eschatin which was generously supplied by Parke, Davis and Co.

In one dog (2–64, figure 12) one adrenal was first removed and the main artery of the kidney on this side was constricted 12 days later. The blood pressure rose significantly, showing the responsiveness of the blood pressure of this animal. At the height of elevation of the blood pressure, the second adrenal was excised and the main renal artery of the corresponding side was permanently constricted. Instead of rising to a higher level, or at least remaining elevated, the blood pressure soon fell to a level below the previous normal for this animal and it died in 11 days of acute adrenal insufficiency.

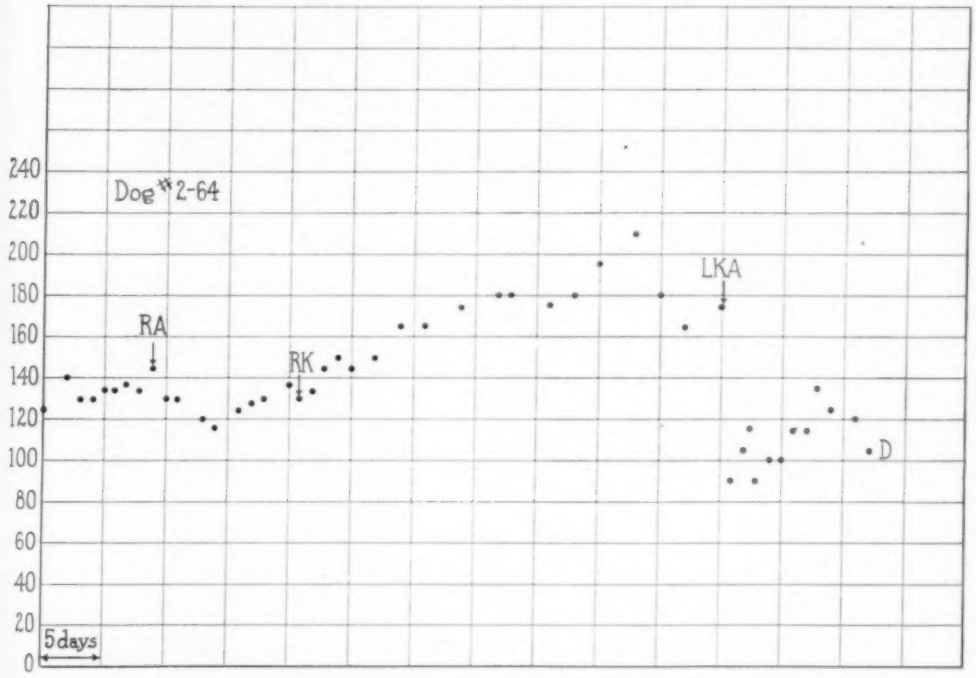

FIGURE 12. Dog 2-64. Female. 18.8 Kg.

● = Mean blood pressure, mm. Hg. RA = Right adrenalectomy. RK = Right main renal artery severely constricted. The blood pressure became significantly elevated. LKA = Left adrenalectomy and left main renal artery moderately constricted. The blood pressure fell to below normal level and the animal died of acute adrenal insufficiency. D = Died.

The results of these experiments show that bilateral adrenalectomy, without supportive or substitution therapy, interferes with the development and maintenance of hypertension which usually follows the production of renal ischemia.

Bilateral Adrenalectomy with Supportive Treatment and Renal Ischemia. It has been shown that the life of bilaterally adrenalectomized animals can be prolonged by the administration of sodium chloride [121-124] or sodium chloride and sodium bicarbonate or sodium citrate.[125]

In one dog (2–89, figure 13), the constriction of the main renal artery was carried out on the same side and at the same time as the first adrenalectomy. After this the blood pressure became significantly elevated, which demonstrated the responsiveness of the blood pressure of this animal to the effect of renal ischemia. At the end of four weeks, while the blood pressure was still elevated, the second adrenal was removed and the main artery of the kidney on the same side was constricted. Supportive treatment in the form of sodium chloride alone was given by stomach tube during the first 10 days and then sodium bicarbonate was added. After the second adrenalectomy and constriction of both main renal arteries, instead of rising to a higher level, the blood pressure gradually fell to a level below the normal for this animal and death occurred in 19 days.

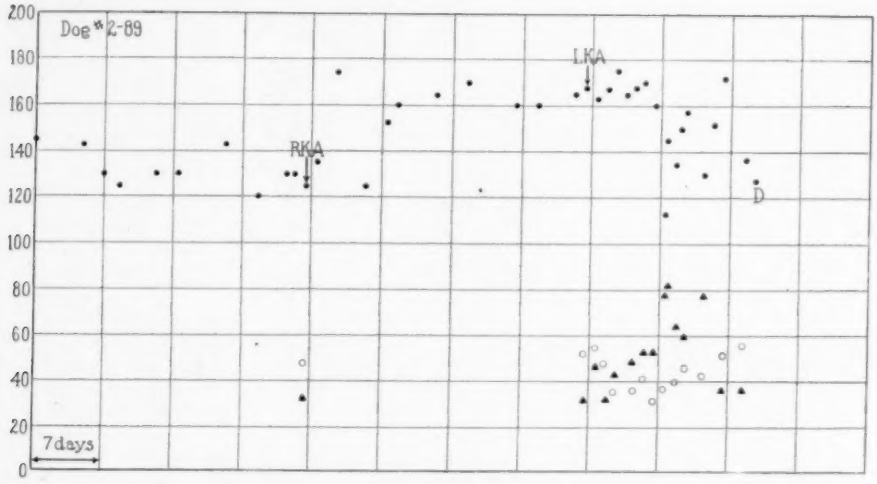

FIGURE 13. Dog 2–89. Male. 17.6 Kg.

● = Mean blood pressure, mm. Hg. ○ = CO_2 combining power, volumes per 100 c.c. plasma. ▲ = Non-protein nitrogen mg. per 100 c.c. plasma. RKA = Right adrenalectomy and right main renal artery moderately constricted. After this the blood pressure showed a moderate elevation. LKA = Left adrenalectomy and left main renal artery moderately constricted. From the time of the second adrenalectomy this animal received sodium chloride (0.75 gm. per kg. of body weight) by stomach tube for 9 days and from then on received in addition sodium bicarbonate (0.25 gm. per kg. of body weight). There was no greater elevation of blood pressure following the clamping of the second renal artery and the blood pressure gradually fell to below the original level. D = The animal died of acute adrenal insufficiency.

In another dog (2–81) the constriction of both main renal arteries was carried out at the same time as the bilateral adrenalectomy. This was followed by the administration of supportive treatment in the form of sodium chloride and sodium citrate by mouth. The animal survived 15 days but the blood pressure did not become elevated during that period. It fell gradually to a low level and the animal died of acute adrenal insufficiency.

The most convincing proof that in bilaterally adrenalectomized animals supportive treatment alone is not sufficient to permit elevation of blood

pressure or maintenance of elevated blood pressure due to renal ischemia was furnished by four dogs *2–77*, *2–87*, *2–88* and *3–08* (figures 14 to 17). These animals received both supportive and substitution therapy after the second adrenalectomy but after a varying length of time the administration of cortical extract was discontinued for varying periods. As a result, some of the animals received only supportive treatment in the form of sodium chloride and sodium bicarbonate or sodium citrate by stomach tube for as long as six weeks. In some of these animals the blood pressure remained at the normal or elevated level for a while, but invariably the blood pressure fell to a lower level and rose again to the normal level or higher only when the administration of cortical extract was resumed. These results show that bilateral adrenalectomy, even if followed by supportive treatment, interferes with the development and maintenance of the hypertension which is usually produced by renal ischemia.

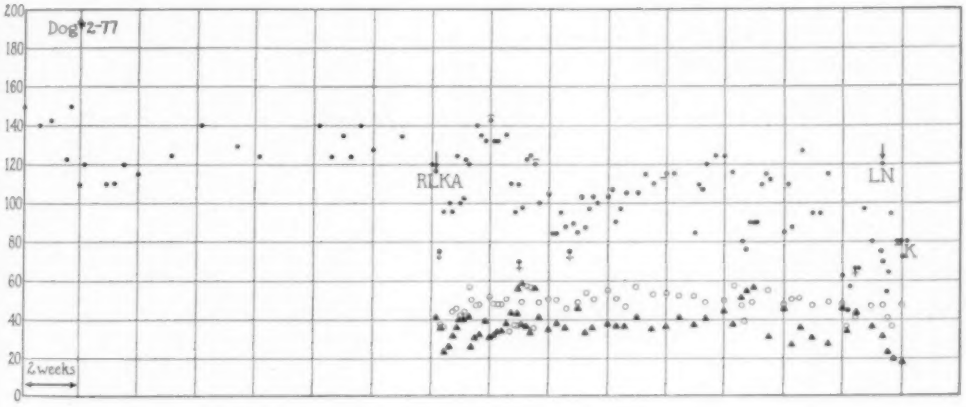

FIGURE 14. Dog *2–77*. Female. 11.4 Kg.

● = Mean blood pressure, mm. Hg. ▲ = Non-protein nitrogen, mg. per 100 c.c. ○ = CO_2 combining power, volumes per 100 c.c. RLKA = Bilateral adrenalectomy and both main renal arteries moderately constricted. LN = Left nephrectomy. + = Intravenous adrenal cortical extract begun. — = Adrenal cortical extract discontinued. During the entire period following the bilateral adrenalectomy the animal received by stomach tube, in two equal doses (9:00 a.m. and 4:00 p.m.) a total of 0.75 gm. per kg. of body weight of sodium chloride and 0.25 gm. per kg. of body weight of sodium bicarbonate. At no time during the four months of survival did the animal show elevated blood pressure. Several times, when cortical extract was discontinued, the blood pressure fell to very low levels. K = Killed.

Bilateral Adrenalectomy with Supportive and Substitution Treatment and Renal Ischemia. In Dog *2–77*, both adrenals were excised and at the same time both main renal arteries were permanently constricted (RLKA, figure 14). During the entire four months of survival following these operations the animal received supportive treatment daily in the form of sodium chloride and sodium bicarbonate by stomach tube and intermittent substitution treatment in the form of intravenous cortical extract. Im-

mediately after the operation the administration of adrenal cortical extract was begun (+, figure 14). At intervals, for varying periods, the administration of cortical extract was discontinued. The blood pressure remained at about the normal level during the periods when the cortical extract was also being administered. When the cortical extract was discontinued (—, figure 14) the mean blood pressure gradually fell to a low level. When the administration of cortical extract was resumed, the blood pressure rose again but never above the normal level. This was repeated several times with the same result. At no time was the pressure in this animal above normal.

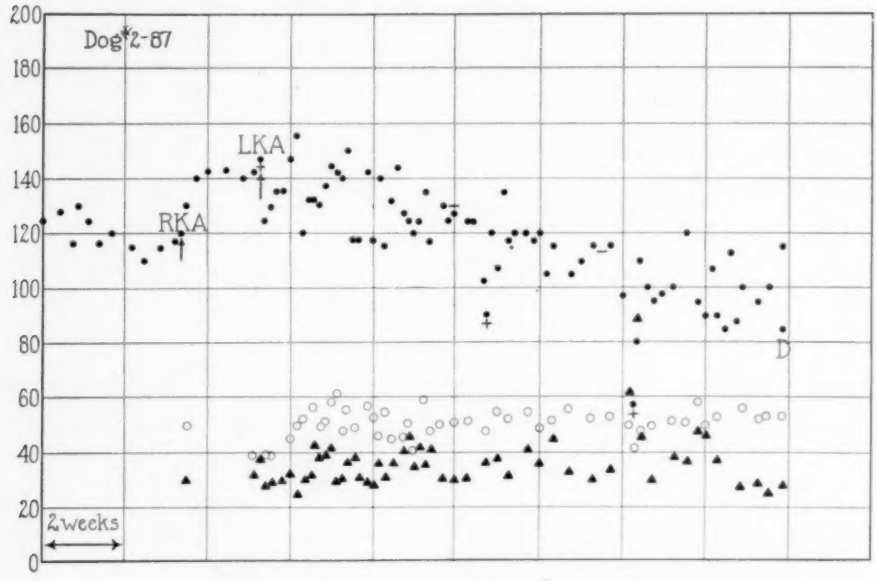

FIGURE 15. Dog 2–87. Female. 12.8 Kg.

● = Mean blood pressure, mm. Hg. ○ = CO_2 combining power, volumes per 100 c.c. ▲ = Non-protein nitrogen, mg. per 100 c.c. + = Intravenous adrenal cortical extract begun. — = Intravenous adrenal cortical extract discontinued.

Sodium chloride (0.75 mg. per kg. of body weight) and sodium bicarbonate (0.25 gm. per kg. body weight) were given during the entire period following the second adrenalectomy. RKA = Right adrenalectomy and right main renal artery moderately constricted. The blood pressure rose moderately. LKA = Left adrenalectomy and left main renal artery severely constricted. From this time the blood pressure gradually fell to a low level despite the supportive and substitution therapy. D = Died.

In dog 2–87 (figure 15) unilateral adrenalectomy and constriction of the main renal artery on the same side were first carried out. After this first operation no supportive or substitution therapy was given. Definite though slight elevation of blood pressure followed this procedure, which demonstrated the responsiveness of the blood pressure of this animal to renal ischemia. After the second adrenalectomy and constriction of the corresponding main renal artery, both of which were performed at the

same time, about two weeks after the first adrenalectomy, supportive and substitution treatment were begun. The blood pressure remained elevated for a while but it did not rise to a higher level and, despite the treatment, gradually fell to below the previous normal.

In two dogs (2–88 and 3–08), one adrenal and the kidney on the same side were first removed. After an interval, the second adrenal was removed and the main artery of the only remaining kidney was constricted. During the entire period after the second adrenalectomy, these animals were given supportive treatment in the form of sodium chloride and sodium citrate by stomach tube. Immediately after the second adrenalectomy the administration of intravenous adrenal cortical extract was also begun. At intervals, for varying periods, the administration of cortical extract was

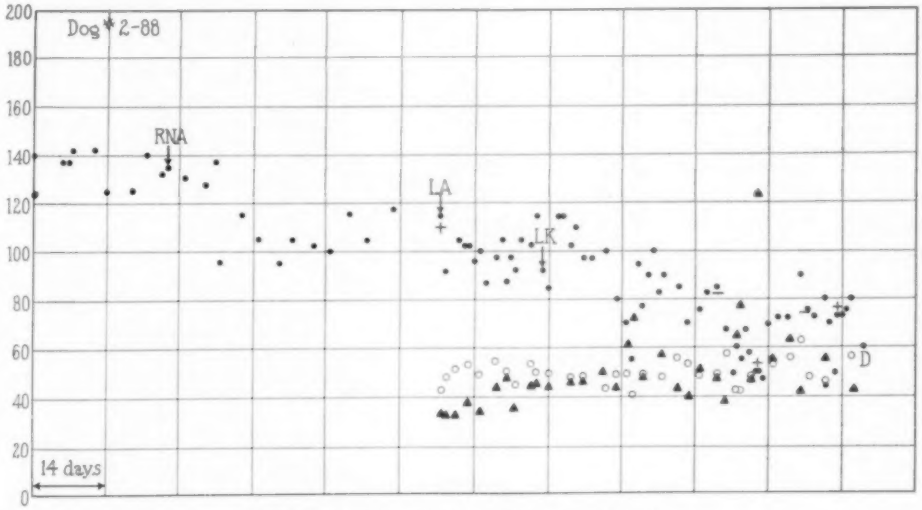

FIGURE 16. Dog 2–88. Female. 16.8 Kg.

● = Mean blood pressure, mm. Hg. ▲ = Blood non-protein nitrogen mg. per 100 c.c. of plasma. ○ = CO_2 combining power of blood, volumes per 100 c.c. of plasma. RNA = Right nephrectomy and adrenalectomy. LA = Left adrenalectomy. LK = Left main renal artery moderately constricted. + = Intravenous adrenal cortical extract begun. — = Intravenous adrenal cortical extract discontinued.

After the left main artery was constricted (LK) the blood pressure gradually fell to a very low level despite the intravenous adrenal cortical extract which was given for long periods at a time and the sodium chloride and sodium citrate which were given by stomach tube twice daily during the entire period following the second adrenalectomy. D = Died.

discontinued. In dog 2–88 (figure 16), the main artery of the only remaining kidney was constricted about two weeks after the second adrenalectomy. There was no elevation of mean blood pressure following this procedure but instead the blood pressure fell gradually to a low level despite supportive and substitution therapy. When the cortical extract was discontinued, the blood pressure fell to even a lower level. The animal survived the second adrenalectomy about 12 weeks. During the intervals when cortical extract was discontinued, the mean blood pressure fell to unusually

low levels and rose again, but not even to the original level, when cortical extract was resumed. In the other dog, 3–08 (figure 17), the constriction of the main artery of the remaining kidney was carried out at the time of the second adrenalectomy. Definite elevation of mean blood pressure followed for a period of about one month. During this entire time intravenous adrenal cortical extract was given daily in addition to the salt and

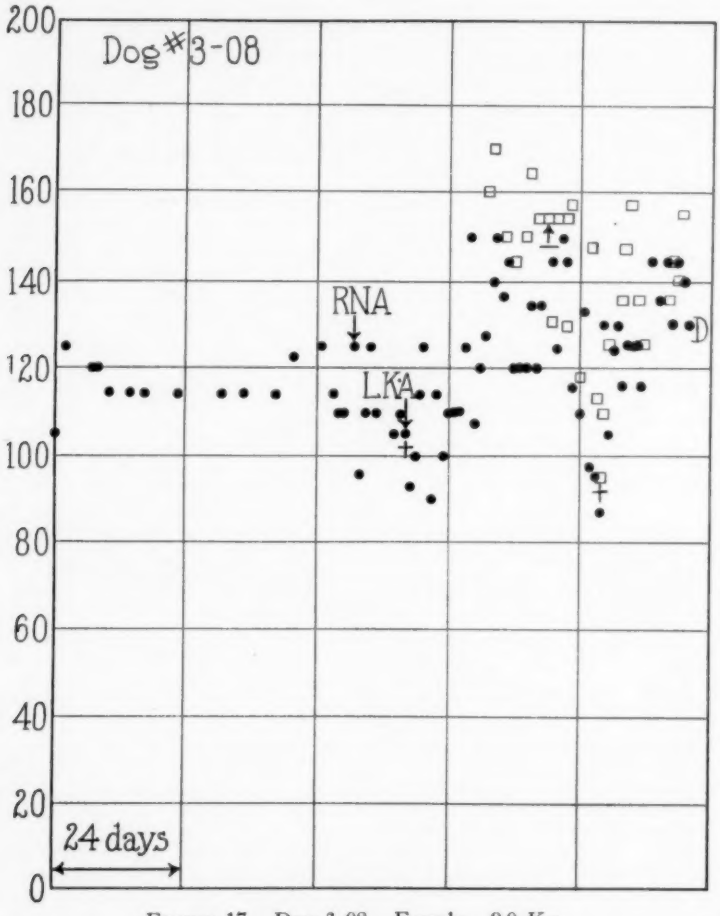

FIGURE 17. Dog 3–08. Female. 9.0 Kg.

● = Mean blood pressure, mm. Hg. Determinations made in a.m. □ = Mean blood pressure, mm. Hg. Determinations made in p.m. 5 hours after the administration of the morning dose of cortical extract, sodium chloride and sodium citrate. RNA = Right adrenalectomy and right nephrectomy. LKA = Left adrenalectomy and left main renal artery severely constricted. + = Intravenous cortical extract begun. — = Intravenous cortical extract discontinued.

Sodium chloride and sodium citrate by stomach tube were given daily during the entire period after the second adrenalectomy.

The blood pressure became moderately elevated and remained elevated for one month during which the dog received substitution as well as supportive treatment. Whenever the intravenous cortical extract was discontinued (—) the blood pressure gradually fell to a level below normal. When cortical extract was begun again (+) the blood pressure gradually rose but did not reach the previous hypertensive level. D = Died of pneumonia.

sodium citrate by stomach tube. When the cortical extract was discontinued at the end of one month, the blood pressure gradually fell to a lower level. When the administration of cortical extract was resumed the blood pressure again became slightly elevated. The animal was accidentally exposed to cold and died of pneumonia.

Up to the present time, definite elevation of blood pressure due to renal ischemia has occurred in one other bilaterally adrenalectomized animal (Dog 2–96) that received substitution and supportive treatment. This animal survived the second adrenalectomy only 19 days. After the constriction of one main renal artery, which was performed eight days after the second adrenalectomy, there was a definite elevation of the blood pressure. Six days later, while the blood pressure was still elevated the main artery of the other kidney was constricted but the animal died the next day.

These results show that, even in the absence of both adrenals, provided adequate substitution and supportive treatment are given, some dogs do develop a significant but not great elevation of blood pressure due to renal ischemia. Without substitution treatment such animals do not develop or maintain hypertension due to renal ischemia.

Renal Ischemia in Dogs with No Adrenal Medulla and Only a Small Remnant of Adrenal Cortex. Additional evidence that adrenal cortical hormone is necessary for the development of hypertension due to renal ischemia is provided by the following experiments.

In one dog (3–12, figure 18) approximately three-fifths of one adrenal was excised and the medulla of the remaining portion removed by means of a curette. At this operation the kidney on the same side was removed. At the second operation, carried out 19 days later, the other adrenal was excised, and the main artery of the only remaining kidney was constricted. In a second dog (3–16, figure 19) exactly the same procedure was carried out but this animal was left with about three-fifths of the cortex alone of one adrenal. There was an interval of 33 days between the two adrenal operations. For a few days following the removal of the second adrenal and constriction of the main renal artery of the only kidney, both dogs received supportive treatment in the form of sodium chloride and sodium citrate by stomach tube. No adrenal cortical extract was given at any time. The blood pressure rose promptly following the production of renal ischemia. Even when the supportive treatment was discontinued, the blood pressure remained elevated and, in 3–16 rose to even a higher level.

These results are interpreted as indicating the preservation of the function of the small portion of adrenal cortex which was left. In both animals, without the aid of supportive or substitution treatment, this small remnant of cortex was sufficient to permit elevation of blood pressure due to renal ischemia. This is additional evidence in support of the view that the hormone of the cortex of the adrenal gland in some way plays a part in the pathogenesis of hypertension due to renal ischemia. More experiments are

being performed in order to elucidate the manner in which this hormone, itself not a vasopressor substance, helps to bring about the pressor effect which follows the production of renal ischemia.

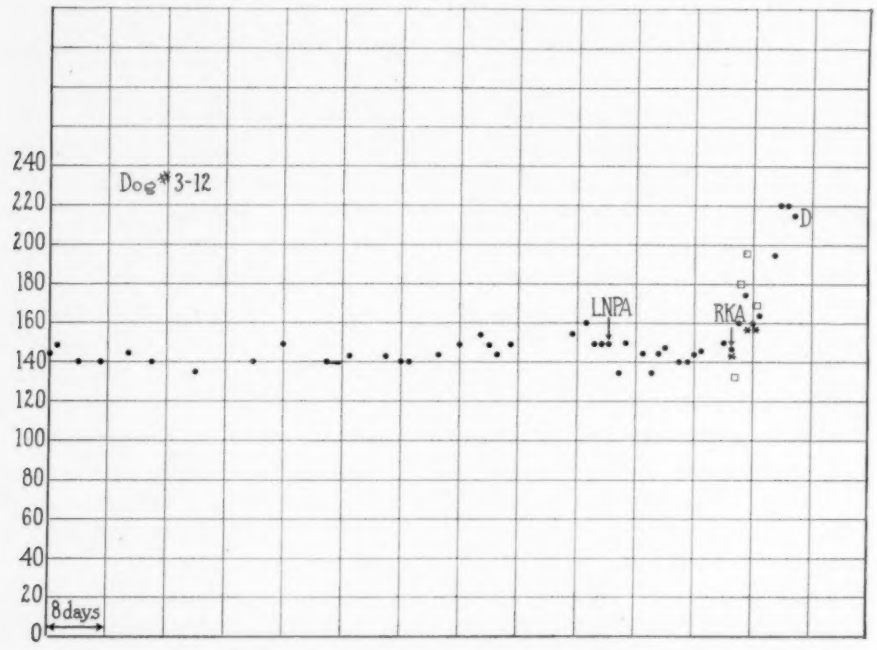

FIGURE 18. Dog 3–12. Female. 11.4 Kg.

● = Mean blood pressure, mm. Hg. LNPA = Left nephrectomy and partial adrenalectomy. The medulla was destroyed. About two-fifths of the cortex was left. RKA = Right adrenalectomy and right main renal artery severely constricted. * = Sodium chloride (0.75 gm. per kg. of body weight) and sodium citrate (0.25 gm. per kg. of body weight) were given by stomach tube from this time on. ** = Sodium chloride and sodium citrate discontinued. No cortical extract was given at any time. The blood pressure rose moderately following the constriction of the renal artery and remained elevated when supportive treatment was discontinued. D = Died.

SUMMARY

The results of the experiments that have been performed up to the present time on the pathogenesis of hypertension due to renal ischemia indicate that the mechanism of the development of this type of hypertension is primarily a humoral one of renal origin.

The failure of the various surgical procedures carried out on the nervous system to affect this type of experimental hypertension is evidently due to the persistence of the renal ischemia which cannot be altered by these procedures as long as the clamps remain applied. These experiments do not in any way controvert the results that have been obtained by the same procedures in the treatment of hypertension in man. They do emphasize, however, the importance of the reduced blood flow to the functioning

components of the kidney as the primary cause of this type of experimental hypertension and perhaps of human hypertension that is associated with arteriolar disease of the kidneys. Since the reduced blood flow in the human kidney is frequently due to narrowing of the arterioles alone, without narrowing of the large arteries, improvement of the circulation

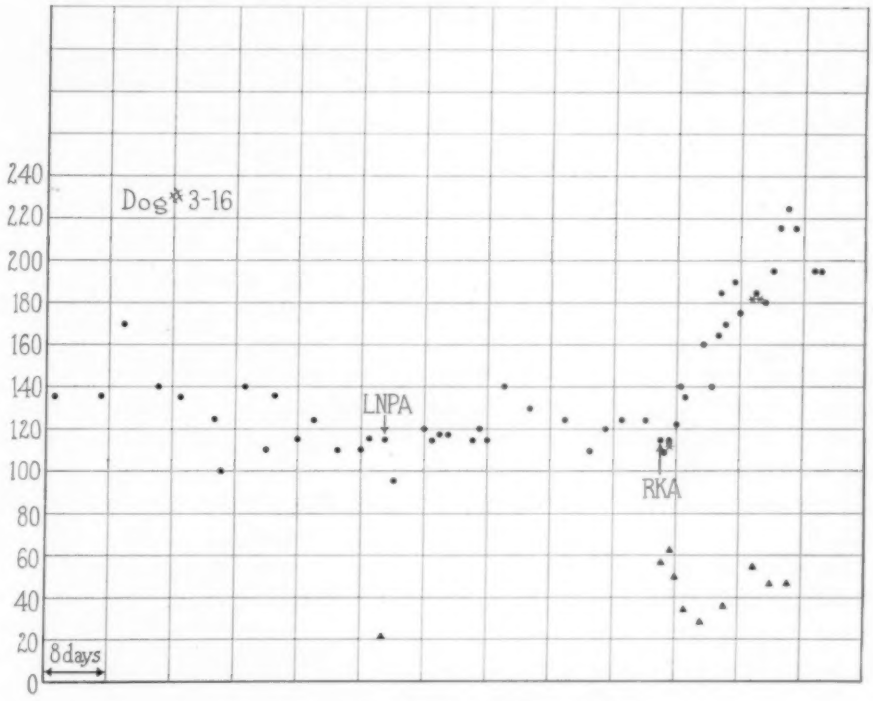

FIGURE 19. Dog 3–16. Female. 14.0 Kg.

● = Mean blood pressure, mm. Hg. ▲ = Non-protein nitrogen, mg. per 100 c.c. plasma. LNPA = Left nephrectomy and partial adrenalectomy. The medulla was destroyed. About two-fifths of the cortex was left. RKA = Right adrenalectomy and right main renal artery severely constricted. * = Sodium chloride (0.75 gm. per kg. of body weight) and sodium citrate (0.25 gm. per kg. of body weight) were given by stomach tube from this time on. ** = Sodium chloride and sodium citrate discontinued. No cortical extract was given at any time. The blood pressure rose moderately following the constriction of the renal artery and remained elevated when supportive treatment was discontinued. The animal is still living.

may result from these procedures on the nervous system due to relaxation of the arterioles in which the organic changes are not fixed. The beneficial effects reported in about the same percentage of cases of hypertension by surgeons using various procedures affecting the vasomotor nervous mechanism in the abdomen may therefore all be due to one cause, the improvement of the circulation through the kidney and not, as has been suggested by some, to the effect on the vasomotor mechanism of a large part of the vascular bed in the abdomen. The latter view has no support in these experiments. Whether or not improved circulation through the kidney is

responsible for the effect should be put to the test by a large series of renal denervations alone in cases of human hypertension. If improvement of the circulation through the kidneys be the common basis of improvement as a result of all of the various surgical procedures that have been carried out, then denervation of the kidneys alone, if it can be accomplished, should give improvement in about the same small percentage of cases of hypertension.

The view that in the pathogenesis of hypertension due to renal ischemia a humoral mechanism involving a hypothetical effective substance of renal origin plays a part of primary importance is based almost entirely upon indirect evidence. Bilateral nephrectomy is not followed by hypertension, yet varying degrees of constriction and even complete occlusion of both main renal arteries are followed by hypertension. This difference is attributed to the absence of a hypothetical effective renal substance when the kidneys are absent. Even when both renal arteries are occluded, the hypothetical effective substance can still be formed and washed into the renal veins by the accessory circulation through the capsule. The constriction or occlusion of both main renal arteries, when accompanied by occlusion of the main renal veins, is not followed by the development of hypertension. This is interpreted as being due to interference with the entrance of the hypothetical effective substance into the circulation. Release of the constriction of the renal arteries, by unscrewing or removing the clamps, causes a prompt return of the blood pressure to normal. The release of the clamp on the main renal artery of only one of two ischemic kidneys is also followed by return of the blood pressure to normal, but it takes longer for the blood pressure to reach the normal than when both clamps are released. This is in keeping with the finding that the clamping of one main renal artery causes only a temporary rise of blood pressure for a varying period. Excision of the ischemic kidney at the height of the hypertension which follows constriction of one main renal artery is also followed by prompt return of the blood pressure to normal. These experiments indicate that if one or two normal kidneys could be transplanted into an animal with hypertension due to renal ischemia, the blood pressure would return to normal because the source of the effective renal substance would be eliminated. Such a study is being carried out at the present time in collaboration with Doctor J. R. Kahn and Doctor W. B. Wartman. Up to the present time the only direct evidence suggestive of the existence of an effective substance has been the demonstration by other investigators [11, 13] of an increased amount of pressor substance in ischemic kidneys as compared with normal ones.

Various experiments that have been carried out on the effect of complete adrenalectomy, with and without supportive and substitution therapy, and the effect of a small remnant of adrenal cortex only on the prevention or maintenance of hypertension due to renal ischemia, indicate that the medulla plays no part, but that the cortex of the adrenal gland may play an important part in the mechanism of development of this type of hypertension

Complete bilateral adrenalectomy, without supportive or substitution therapy, interfered with the development of this type of hypertension. Even with supportive treatment, but without substitution therapy, the animals failed to develop or to maintain hypertension due to renal ischemia. In several bilaterally adrenalectomized animals, however, moderate hypertension did develop when adequate supportive and substitution therapy was given. Because of this and because an amount of cortex close to the minimum requisite for survival and even the absence of both adrenals, if supplemented by the administration of cortical extract, still permitted the development of hypertension due to renal ischemia, the rationale of partial adrenalectomy which has been proposed and practised [127-133] for the treatment of hypertension is questionable to say the least, except in cases of suprarenal tumor [134-140] with hypertension in which the improvement results from the removal of the tumor in the adrenal.

The exact way in which the adrenal cortical hormone acts in conjunction with the hypothetical effective renal substance in the development and maintenance of hypertension due to renal ischemia has not been elucidated. Although the cortical hormone is not by itself a vasopressor substance, yet it may prepare the arteriolar musculature for the action of the hypothetical effective renal substance, or the reverse may be the case. The two may even combine before exerting their synergistic effect on the arteriolar musculature or they may act in conjunction with other hormones. These various possibilities are now being investigated.

Conclusions

Persistent hypertension has been produced in animals (dog and monkey) by constricting the main renal arteries, which reduces the blood flow to the functioning components of the kidneys (renal ischemia).

Hypertension without or with disturbance of renal function, resembling in this respect the benign and malignant types, respectively, in man, can be produced by varying the degree of constriction of the renal arteries.

The results of various experiments indicate that this type of experimental hypertension is due primarily to a humoral and not to a nervous mechanism initiated by the ischemia of the kidneys.

The nature of the effective substance responsible for inducing the hypertension has not yet been elucidated.

The present indication is that the adrenal cortical hormone plays a part in conjunction with the hypothetical effective substance of renal origin in the pathogenesis of hypertension due to constriction of the main renal arteries.

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AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR OF DOCTOR JOSEPH HERSEY PRATT

THE NATURE OF THE CARDIOVASCULAR DISTURBANCES IN NUTRITIONAL DEFICIENCY STATES (BERIBERI) *

By SOMA WEISS, M.D., F.A.C.P., and ROBERT W. WILKINS, M.D.,
Boston, Massachusetts

DURING the past half century significant advances have been made in our knowledge of the etiology of valvular heart disease. Likewise, the recognition of the rôle of arterial hypertension, coronary disease, rheumatic myocarditis, adhesive pericarditis, hyperthyroidism, diphtheria and other infectious diseases has enabled clinicians to account for the majority of instances of non-valvular myocardial disease. There remain, nevertheless, a considerable number of patients who present manifestations of myocardial failure without valvular disease or any recognized type of myocardial disease. We have been prone to diagnose such obscure cases as "arteriosclerotic," "coronary" or "hypertensive" heart disease. A rigid scrutiny of evidence, however, including postmortem examination, often fails to corroborate the clinical diagnosis. Hence they remain "idiopathic." These obscure instances of myocardial failure probably include a number of diseases of varied etiology, as yet unrecognized. It is the purpose of this presentation to describe one type of cardiovascular dysfunction, heretofore generally unrecognized in this country, in which nutritional factors play a causative rôle.

It has been suggested by Shattuck,[1] Wechsler,[2] Minot, Strauss and Cobb [3] and others that in certain types of polyneuritis a nutritional deficiency and particularly deficiency of vitamin B (B_1) plays an etiological rôle. These studies, however, raised the following question: If alcoholic polyneuritis, polyneuritis of pregnancy and certain other neuritides are related to nutritional deficiencies, and particularly deficiency of vitamin B_1, why are they not associated with other manifestations, namely cardiovascular dysfunction such as occurs in patients with beriberi in other parts of the world? Soon after this question was raised we encountered in our wards two patients with nutritional deficiency polyneuritis, who suffered in addition from a severe degree of "idiopathic" circulatory failure. We therefore undertook a study of (*a*) the clinical characteristics of this condition; (*b*) the

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From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston.

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physiological, chemical and morphological changes; (*c*) the etiology; and (*d*) therapeutic measures. A summary of the first part of this investigation was presented before the 1936 meeting of the Association of American Physicians.[4]

Material and Method of Study

In order to determine whether the disease exists as a clinical problem, we undertook an analysis of the records of some 900 patients suffering from various types of nutritional deficiency, including general malnutrition, chronic alcoholism with or without polyneuritis, pellagra, neuritis of pregnancy and diabetes. In this group we discovered 85 cases in which cardiovascular dysfunction of varying severity could not be ascribed to the usual etiological factors. Because all instances in which organic lesions of the cardiovascular system existed were eliminated and because many of the cases were observed by physicians not experienced in cardiovascular problems, the number selected must be considered as minimal. This conclusion is corroborated by the fact that within a period of two years we have personally studied 35 patients from a total of 5,506 admissions to two general medical services in this hospital. The observations here presented are therefore based on a total group of 120 cases.

Observations

Nature and Pathogenesis of Cardiovascular Dysfunctions

Age and Sex Incidence. The ages of the 120 patients varied between 24 and 67 years; 84 per cent fell in the age group 30 to 59 years. Eighty-two per cent were males and 18 per cent females. This age and sex incidence can, however, be considered but an approximation, since the majority of the cases have been gathered from available records and numerous elderly patients were eliminated because of the simultaneous presence of hypertension or arteriosclerosis.

Nutritional History. The majority of the patients were heavy consumers of alcohol. A smaller group gave a history of unbalanced diet as a result of psychic peculiarities ("food cranks"), of drug addiction, of medical restriction of diet or of persistent nausea, such as is present in pregnancy. In relatively few patients poverty played a rôle. The caloric intake was adequate or more than adequate in the majority, as was also indicated by their weight. Reliable detailed history was obtainable in only a small group. The estimated vitamin B (B_1) intake in this group was less than that indicated by Cowgill as liable to produce polyneuritis. There were a few patients, on the other hand, in whom both the caloric and the estimated vitamin B (B_1) intake were adequate. In this group there were usually indications of digestive dysfunction, suggesting lack of proper absorption or utilization of the essential food substances.

Symptoms and Signs of Non-Cardiovascular Origin. Cardiovascular

abnormalities were present in the majority of instances, along with other recognized manifestations of nutritional deficiency and particularly with those of "beriberi" and pellagra. In a smaller group scurvy was present. In some instances, however, circulatory failure was the sole manifestation. Table 1 shows the associated signs not referable to the cardiovascular system. In a given patient one or more of these signs were present in various combinations, but peripheral neuritis, gastrointestinal disturbances and psychosis were most frequent.

TABLE I

Non-Circulatory Manifestations

Peripheral neuritis	Hypoproteinemia
Psychosis	Optic neuritis
Glossitis	Dysphagia
Constipation	Hoarseness
Diarrhea	Aphonia
Dermatitis	"Spooned" nails
Anemia	Purpura

Symptoms and Signs Referable to the Cardiovascular System. The clinical symptoms and signs referable to the cardiovascular system are presented in table 2. The most frequent combinations of symptoms and signs

TABLE II

Circulatory Manifestations

Symptoms	
Tachycardia with palpitation	Prominent cardiac pulsation
Fatigability	Pulmonary râles
Dyspnea on exertion	Engorged veins
Cough	Gallop rhythm
Edema	Warm extremities
Orthopnea	"Pistol" sounds
Paroxysmal dyspnea	Dilated heart
	Cyanosis
Signs	Syncope
Tachycardia	Circulatory collapse
Embryocardia	Bronchopneumonia
Systolic murmurs	Diastolic murmurs

were dyspnea on exertion with tachycardia and embryocardia; palpitation with gallop rhythm; prominent cardiac and epigastric pulsations; bounding peripheral pulses with sounds ("pistol shots"), particularly over the carotid, subclavian and femoral arteries; and edema, both diffuse and dependent, with distended veins. The skin was often flushed and warm. In 24 patients selected for special study, the cardiovascular disturbance was severe and, at times, extreme.

The *heart* was normal in size or enlarged. There was usually a prominent precordial pulsation with a rapid systolic rise and diastolic fall. At times the extensive thoracic pulsations over the heart suggested cardiac enlargement, but this was not always corroborated by roentgenological examination. The heart rate was usually rapid. Under rest and dietary

treatment the tachycardia returned to the normal level, either slowly or rapidly. In the latter case transient bradycardia frequently followed.

The character of *dyspnea* varied considerably. In the majority of patients dyspnea occurred only on slight or moderate exertion. In some, continuous dyspnea and orthopnea developed. Several patients without evidence of pulmonary infection complained of an irritating, dry "hacking" cough, particularly annoying at night. Patients with typical attacks of cardiac asthma (paroxysmal dyspnea) were also encountered. In some instances attacks of dyspnea appeared with unexpected suddenness in patients who had been in vigorous health. Such attacks were also observed in bed-ridden patients. Signs of pulmonary congestion were frequently present, and cloudiness of the lung fields was seen on roentgenological examination. Patients with severe polyneuritis were less liable to have advanced failure of the circulation. The most plausible explanation for the infrequent coexistence of the two conditions seems to be that the polyneuritis prevents muscular exertion.

The *arterial pressure* was usually normal with a tendency to increased pulse pressure. In some cases the systolic pressure was moderately elevated during the acute stage of circulatory failure, but it returned to normal when the patient's condition had improved. The *venous pressure* was elevated or normal.

Edema was present in one group of patients. In some it was of extreme degree and diffuse, in others only dependent in type. Often at the time of admission the severity and extent of edema were not appreciated. A patient with full, round facies and robust appearance rapidly changed to a thin-faced individual with a delicate bodily structure. Decreases in the osmotic pressure of the blood, even when present, could not be held responsible because the edema often disappeared while the osmotic pressure remained essentially unchanged. The protein content of the edema fluid was low (Cases 1, 2 and 4).

Attacks of *syncope* were observed in five patients. The attacks were associated with asystole and fall in the arterial pressure, and they could be induced by stimulation of the carotid sinus. The hyperactive carotid sinus reflex in these patients was of the vagotonic type. Following the administration of a diet rich in vitamin B (B_1), the irritable state of the carotid sinus reflex subsided and in four cases stimulation of the sinus subsequently produced no symptoms and no asystole. The fifth patient developed an acute psychosis and was transferred to another institution.

Circulatory collapse developed in some of the patients with congestive failure of the circulation. In other instances in which it occurred the only premonitory sign was tachycardia.

Patients with severe congestive failure of the circulation were especially prone to develop *fever*. The condition of these patients often became much more serious with the onset of an elevated temperature. In some cases the

fever seemed to have precipitated the congestive failure; it is equally plausible, however, that the reverse was true. Signs of bronchopneumonia were often detected, but sometimes the cause of fever remained obscure even after postmortem examination.

Electrocardiographic Studies. Electrocardiograms taken in 67 cases with normal blood pressures and with no clinical evidence of organic heart disease disclosed abnormalities in all but five cases (table 3). Figures 8,

TABLE III

Electrocardiographic Findings in 67 Cases

	No. of Cases	% of Total
Normal records	5	7
Abnormal records	62	93
Change in direction of T-wave	46	68
Sinus tachycardia (100 or over)	42	63
Prolonged Q–T (electrical systole)		
Above Cheer Li standards (Upper limit of K: Males 0.38, females 0.42)	53	79
Above Shipley-Hallaran standards (Upper limit of K: Males 0.43, females 0.45)	30	45
Ventricular premature beats	10	15
Auricular premature beats	9	13
Low voltage of QRS (below 5 mm.)	6	9
Auricular fibrillation	3	4
Intraventricular block	3	4

11, 12, and 15 are examples of the electrocardiographic changes observed. These changes occurred in patients with nutritional deficiency, or with clinical polyneuritis, pellagra, psychosis, or combinations of these syndromes. In some instances no other clinical manifestations of deficiency disease existed. Not all patients with the same type of nutritional deficiency had changes in the electrocardiograms, nor were they present in all instances of polyneuritis or pellagra. No explanation can be offered for their absence in patients with apparently the same underlying disease. The electrocardiographic changes disappeared with improvement after the administration of a diet rich in vitamin B or of crystalline vitamin B_1. Patients were also observed in whom the abnormality of the electrocardiogram appeared or became accentuated immediately after administration of vitamin B_1 or of food rich in vitamin B (B_1), only to disappear eventually.

Hemodynamics of the Circulation. In 13 patients technical measurements of the circulation were made. The velocity of the blood flow, the oxygen difference of the blood in the femoral artery and vein, the vital capacity of the lungs and the venous pressure in the antecubital and femoral veins were usually measured on several occasions. The most significant finding was that patients with enlarged heart, rapid heart rate, gallop rhythm, dyspnea, orthopnea, generalized edema, low vital capacity and elevated venous pressure had a normal or increased velocity of blood flow and a low arteriovenous oxygen difference. Such behavior of the circulation differs from that in other types of organic heart disease in which there

generally exists a direct relationship between the degree of congestive failure and the slowing of the blood flow.[5, 6]

The rapid blood flow confirmed the clinical impression created by the warm extremities, the flushed color, the bounding pulses and the increased arterial pulse pressure, namely, that there was a *generalized arteriolar dilatation.* This is an important factor in the clinical picture. Indeed, after treatment with vitamin B_1 one of the most constant and dramatic effects was the slowing of the circulation to a normal, or temporarily even to a subnormal level. The beneficial effect in lowering peripheral capillary pressure and thereby enhancing the removal of edema fluid by the venules was demonstrated in several patients who had diuresis following this slowing, while the osmotic pressure of the blood and the venous pressure remained unchanged (Cases 2, 3 and 4). Arteriolar constriction following B_1 therapy must also react, in turn, centrally on the heart in the same beneficial manner as the closing of an arteriovenous aneurysm.[7]

With improvement after vitamin B_1 therapy the heart rate slows, the gallop rhythm subsides and the size of the heart returns to normal. The elevated venous pressure falls, the vital capacity increases and the edema, orthopnea and dyspnea disappear. A simultaneous study of the heart, peripheral vascular system and circulation indicates that the failure of the circulation in patients with nutritional deficiency depends on the combined effects of dilatation of the peripheral arteriolar system and myocardial failure.

While some of the patients exhibited the syndrome of pure *right ventricular failure,* this was not the characteristic manifestation. There were generally symptoms and signs of *left ventricular failure* as well. Moreover, patients with only pulmonary congestion and edema, exhibiting attacks of paroxysmal dyspnea, were also observed. In some patients rapidly developing *circulatory collapse* or shock dominated the clinical picture. Our observations, therefore, fail to reveal a rigid circulatory syndrome. In general the clinical picture in patients with a severe degree of circulatory failure was characterized by (*a*) good and often rapid peripheral circulation associated with warm skin, high bounding pulse with arterial sounds, and normal or increased velocity of blood flow; (*b*) a failing heart with preponderant right or left ventricular failure, as indicated by high peripheral venous pressure and edema, or by dyspnea, orthopnea, paroxysmal attacks of dyspnea associated with low vital capacity, the physical signs of congestion, and cloudiness of the lung fields in the roentgenogram; (*c*) a tendency to terminal circulatory collapse or shock.

Chemical Changes. Analysis of the blood chemistry revealed the following trends: (*1*) Moderate lowering of serum proteins and colloid osmotic pressure; (*2*) normal or moderately increased non-protein nitrogen; (*3*) moderate elevation of fasting blood sugar; (*4*) normal carbon dioxide capacity; (*5*) increase in bisulphite binding substances.[8] The urine analyses showed tendency to ketosis, and occasional glycosuria.

Organic Heart Disease and Nutritional Deficiency

An especial attempt was made to study cardiac and circulatory disturbances in relation to nutritional deficiencies in their pure form. Whether nutritional factors play a rôle in patients with organic cardiovascular disease was not the main interest of the investigation. This problem is particularly difficult because of the two simultaneously existing major variables and because no objective index is available for measuring the specific relationship of circulatory failure to nutritional deficiency. We have encountered patients with hypertensive and chronic rheumatic heart disease, however, in whom a severe degree of congestive failure has been precipitated on repeated occasions by lack of proper food or by the consumption of large amounts of alcohol.

Frequency

The cardiovascular disturbances here described occurred in a ratio of about 1 in 160 admissions to the medical wards. A comparison of the occurrence of this type of cardiovascular dysfunction with the frequency of some of the other diseases of the cardiovascular system indicates that in this hospital the condition is more frequent than congenital heart disease, adhesive pericarditis, hyper- or hypothyroid heart disease, and subacute bacterial endocarditis. The relative frequency of the condition, however, will vary considerably in different strata of society, in different races and in various parts of the country.

Prognosis

Under proper medical management the condition offers a good prognosis in the majority of instances. In the advanced stage, particularly if the deficiency has existed for a long time, the circulatory failure may terminate fatally in spite of treatment. Among the 35 cases personally observed, fatalities due to acute failure of the circulation occurred in four, two of which were untreated. In an additional five cases death was due primarily to other causes. The improvement may be rapid or slow. The determining factors in the rate of improvement have not been established, but the duration as well as the severity of the nutritional deficiency seems to be important. Final recovery is apparently complete in those patients who survive the acute failure.

Differential Diagnosis

The absence of the recognized etiological causes of organic heart disease, on the one hand, and the history of unbalanced diet or digestive dysfunction, on the other, should suggest the possibility that the cardiovascular disturbance is of nutritional origin. If certain non-circulatory manifestations of vitamin deficiency described above are also present, such a possibility is enhanced. The combined presence of congestive failure of the circulation and a relatively or absolutely increased rate of the circulation makes the

diagnosis probable. The assured diagnosis depends on complete recovery of the patient in response to rest, and to diet or extracts rich in vitamin B_1. Some cases of obscure myocarditis may offer difficult differential diagnostic problems. The history of unbalanced diet and of the peripheral vascular signs are of aid in such problems.

Treatment

As in other types of heart disease, evaluation of the efficacy of therapeutic measures is difficult, mainly because of the inadequacy of control observations. Patients with circulatory failure caused by nutritional deficiency kept at rest in bed, with or without digitalis, diuretics and other measures, usually showed a moderate degree of improvement. In three cases, however, severe circulatory embarrassment with collapse indicated the possible harmful effects of such a control period. In 25 patients observed during the past 12 months the usual method of study was as follows: On entrance to the hospital the patient was kept in bed and was given a special diet deficient in " B " vitamins. Usually no medication was given, or occasionally digitalis and diuretics were administered in relatively large doses during a period of from four to seven days. Frequent measurements of various functions of the circulation were made. Following these control observations, all medication was discontinued and vitamin B_1 extract, or, more recently, crystalline vitamin B_1 was administered intravenously, intramuscularly or subcutaneously several times a day for from four to seven days.* During this period the vitamin " B " deficient diet was continued and the measurements and clinical observations were repeated. Subsequently the parenteral administration of vitamin B_1 was replaced by a diet and oral extracts rich in vitamin B_1. The dosage of crystalline vitamin B_1 varied. In the early stage of our studies we used doses of 10 to 20 mg. a day. More recently we have given an average of 50 mg. and as high as 130 mg. a day. Because there is but scant available information on the elimination and storage of vitamin B_1 in the human body, the dosage is necessarily empirical. We have purposely administered considerably larger doses than those indicated by animal experiments.[9]

In spite of the fluctuation of the state of the circulation during the control period, following the administration of extracts or crystals of vitamin B_1, as indicated by the illustrative cases, the improvement was frequently striking. In general the improvement was most rapid in patients with a severe degree of congestive failure. The first change observed was the increased utilization of oxygen and slowing of the blood flow, which occurred in eight cases in which measurements were made within 24 hours following the administration of the first dose of vitamin B_1. These initial

* Two preparations were used for parenteral administration: a highly purified and standardized preparation of vitamin B_1, obtained through the courtesy of the Winthrop Chemical Company, Inc., New York; and crystalline vitamin B_1, obtained through the courtesy of Merck & Company, Inc., Rahway, New Jersey.

changes in the circulation, accompanied by subjective improvement, were followed by a marked degree of diuresis, slowing of the heart rate and decrease in the venous pressure. Simultaneously there was a slow but steady rise in the vital capacity of the lungs and a decrease in cardiac size. The cardiovascular abnormalities last to disappear were those revealed by the electrocardiogram. No untoward symptoms were observed even after such a large intravenous dose of crystalline B_1 as 50 mg. In some patients a temporary elevation of the arterial pressure of several days' duration followed the first course of treatment.

Although our primary interest was the study of cardiovascular dysfunction in relation to nutritional deficiencies, we have had opportunity to observe the response of patients with *polyneuritis* to crystalline vitamin B_1. There was no parallelism between the rate of improvement in the circulatory functions and in the nervous functions. The improvement usually was more striking, rapid and complete in the cardiovascular than in the neurological disturbances. The latter, particularly when chronic, in spite of the large doses of crystalline vitamin B_1, returned only slowly and incompletely toward normal. In a few instances, on the other hand, particularly in the mild cases of short duration, improvement in vibration sense, paresthesias and motor function occurred within two days after treatment was instituted.

Effect of Crystalline Vitamin B_1 on the Non-Deficient Cardiovascular System

Seven patients with no vitamin deficiency were given parenteral crystalline vitamin B_1 in doses ranging from 10 to 120 mg. a day for from one to seven days. In no case was there significant change in any aspect of the heart or of the circulation. In two patients, shortly after injection there occurred temporary minor changes in the electrocardiograms. Four patients had edema on which the vitamin had no diuretic effect. Two patients with clinical signs of B_1 deficiency (polyneuritis) but without cardiovascular dysfunction showed no changes in the heart or circulation following large doses of crystalline B_1. Two patients who initially had had vitamin deficiency and cardiovascular dysfunction of the type described, which returned to normal after the first course of B_1, showed no effect when a second course of vitamin was given several weeks later (Cases 3 and 4).

Morphological Observations

Wenckebach [10] has described microscopical changes in the hearts of patients with "beriberi heart" in Java, which he has claimed are characteristic, if not specific. We have therefore examined sections of the hearts of patients who died as a result of alcoholic and other types of nutritional polyneuritis or pellagra, with or without the type of cardiovascular disturbances described above. Of 30 cases, 19 exhibited cardiovascular dysfunction in addition to tachycardia. Death in these cases was often the

result of sudden circulatory collapse, associated with terminal bronchopneumonia. The myocardial fibers and the conductive bundle of this group exhibited various degrees of "hydropic" degeneration. In addition, intercellular edema and collagen were present. Figures 1, 2, 3, 5, 6, and 7

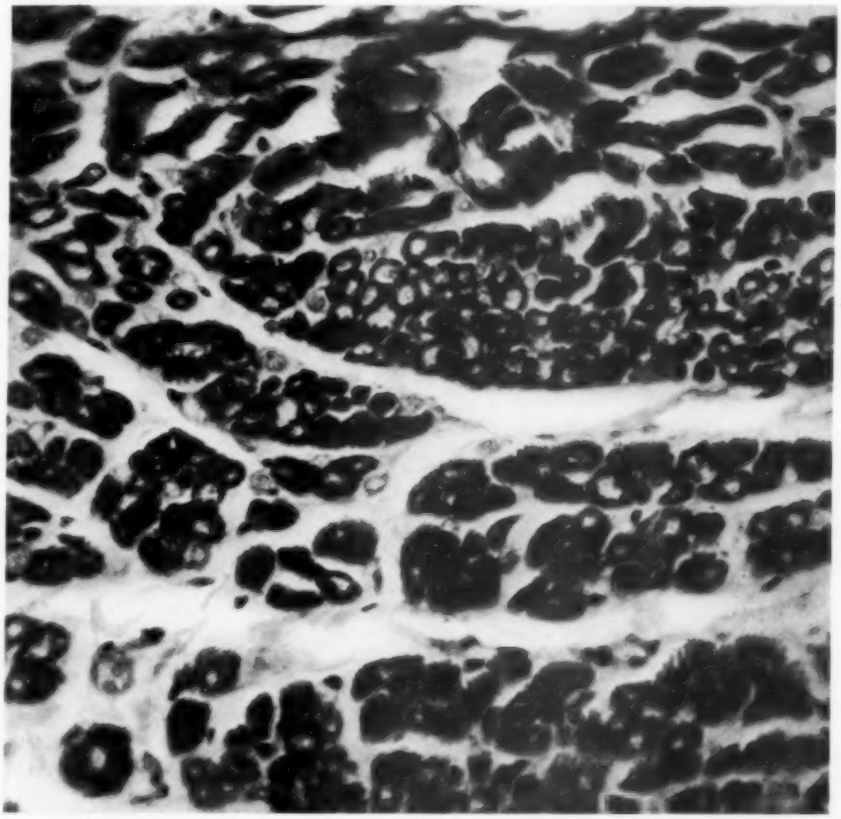

FIG. 1. "Hydropic" degeneration of muscle fibers of the heart with "interstitial edema" in pellagra and polyneuritis. 400 ×.

demonstrate the types of changes observed. No relationship could be found between the degree of histological change and the clinical manifestations. In no instance was there evidence of inflammation.

The sections of the hearts of the group with nutritional deficiency and cardiac failure, as well as of cases with polyneuritis or pellagra without heart failure, have been compared with cardiac sections of two control groups. The first group consisted of eight cases of portal cirrhosis of the liver without manifestations of vitamin deficiency. The second group included 14 cases without heart disease and four cases with fatal organic heart disease. In both control groups there were cases with a moderate degree of "hydropic" degeneration and with interstitial edema similar to that found in the deficient group.

The size of the heart varied. In the majority of instances the weight of the heart was normal, and there was moderate dilatation of the right ventricle. In nine out of 30 cases there was an increase in weight and a considerable degree of dilatation of the cardiac chambers, particularly the right ventricle. In the group observed by us dilatation of the right ventricle

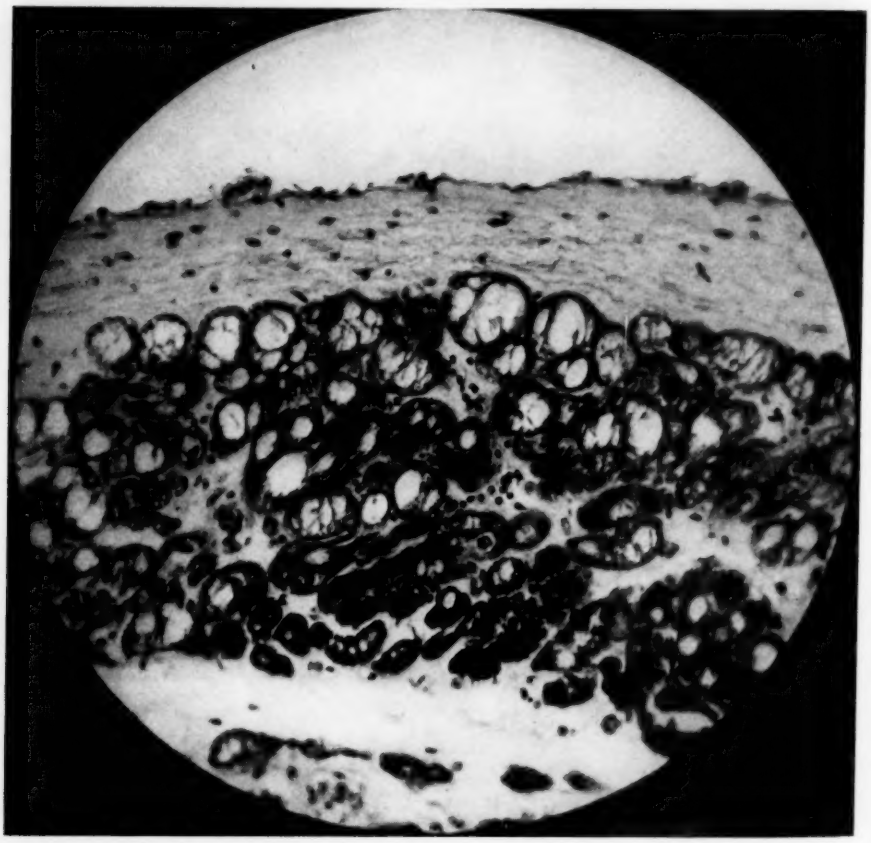

FIG. 2. "Hydropic" degeneration of cross sections of subendocardial conductive fibers in pellagra and polyneuritis. 200 ×.

was not as marked or as frequent as in the group of "beriberi hearts" studied by Wenckebach in Java.[10] The histological changes, on the other hand, were identical with those described by Wenckebach. Our data, in contrast to those presented by Wenckebach, do not indicate that the histological changes observed are specific or even characteristic. They can be present in other diseases.

Sections of the brain revealed swelling of the ganglion cells with marginal displacement of cell nuclei within the vagus centers. In one case there was destruction of the cells with replacement by glia nodules (Dr. L. Alexander).

Water Content of Cardiac and Skeletal Muscles

Aalsmeer and Wenckebach [11] have suggested that deficiency of vitamin "B" produces physicochemical and physiological alterations in the body which lead to water retention in the cardiac and skeletal muscles. They

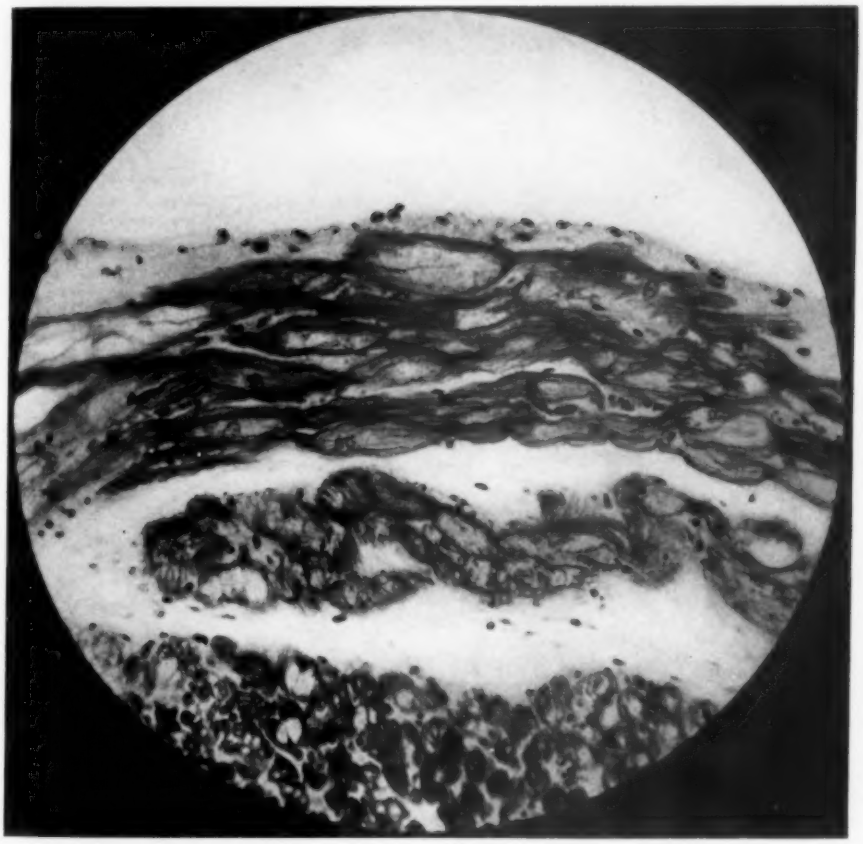

FIG. 3. "Hydropic" degeneration of longitudinal section of subendocardial conductive fibers in pellagra and polyneuritis.

have claimed that the "hydropic" degeneration and interstitial edema are indications of such changes. Wassermeyer [12] reported that the heart of birds deficient in vitamin B contains more water than that of normal animals.

In order to obtain information on this phase of the problem, we have measured the water content of the right and left ventricles and of the abdominal rectus muscle in the following conditions: (*a*) nutritional deficiencies with or without heart failure; (*b*) control group with no heart disease; (*c*) organic heart disease with anasarca.[4] The water content was measured with a gravimetric method. The group with nutritional deficiencies included three patients with combined polyneuritis and pellagra, one

with scurvy and polyneuritis and five with nutritional deficiency, heart failure and cardiac dilatation. No significant difference in the water content of the heart in various groups was observed. It is of interest that even in the group with organic heart disease and with generalized anasarca and with low serum protein, the water content of the myocardium

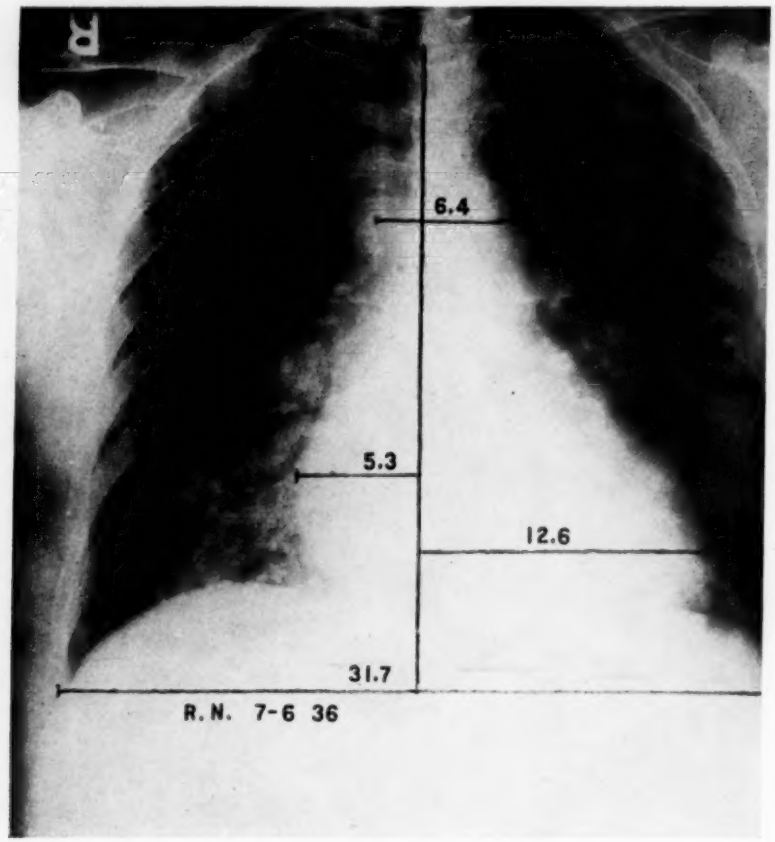

FIG. 4. The cardiac shadow in Case 1.

remained essentially normal. The abdominal rectus muscle, on the other hand, showed at times increased water content in the presence of anasarca.

Case Reports Illustrating Types of Cardiovascular Disturbances and Therapeutic Responses Observed

The following cases are reported in detail as examples of the types of cardiovascular disturbances encountered and of the responses to the therapeutic agents administered. Additional cases have been reported in a previous communication.[4]

Case 1. *Severe congestive failure of the circulation, mild pellagra and polyneuritis, fatal circulatory collapse.* R. N., an odd-job man, aged 36 years, had been drinking ½ pint of alcohol daily for two years, and one pint to one quart a day for three months. He had eaten a grossly inadequate diet which became more deficient the more he drank. He complained of increasing dyspnea on exertion for one month, dependent edema for three weeks, hacking cough for 10 days and orthopnea with insomnia for one day.

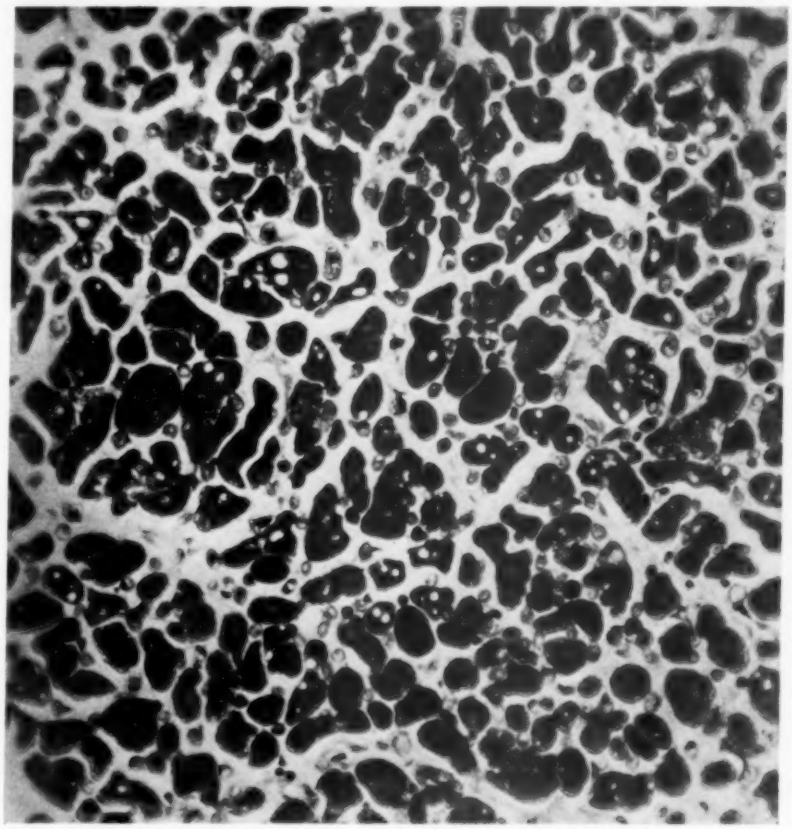

FIG. 5. "Hydropic" degeneration of the muscle fibers in Case 1.

The family history and past history were non-contributory.

Physical examination revealed a well-nourished, slightly jaundiced man with severe orthopnea and diffuse edema, more pronounced in the dependent parts. There was pigmentation and scaliness of the skin on the dorsum of the hands and feet and on the lower legs. The veins of the neck were engorged. The heart was percussed 12 cm. to the left and 5 cm. to the right of the midsternal line. A gallop was heard at the apex and a blowing systolic murmur at the base of the heart. The second sound at the pulmonic area was accentuated. The heart rate was 120 per minute and the rhythm was regular; arterial pressure 110 mm. Hg systolic and 46 diastolic. "Pistol" sounds were audible over the carotid and femoral arteries. The lower third of both lungs posteriorly was dull to percussion, and over these areas and also anteriorly over the left hilar region moist râles were heard. The abdomen was pro-

tuberant and there was shifting dullness in the flanks. A firm liver edge was palpable 4 cm. below the right costal margin. The spleen was not felt. Knee jerks were greatly diminished and ankle jerks were absent. Temperature 98° F. Respirations 36 per minute. Weight 183 pounds (usual weight 160 pounds).

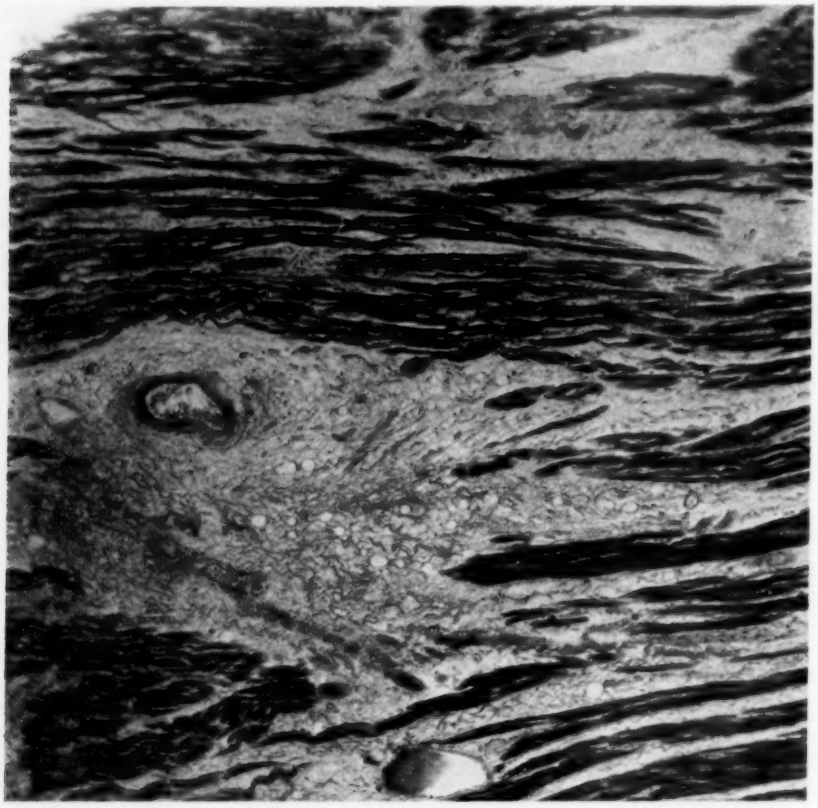

FIG. 6. Perivascular "edema" and separation of the muscle fibers in Case 1.

Laboratory studies: *Urine*, acid, specific gravity 1.025, albumin trace, sugar 0, bile positive; sediment, occasional leukocytes and hyaline casts. *Blood*, hemoglobin 87 per cent, erythrocytes 4,430,000 per cu. mm. Icterus index 14. Total protein content of the plasma 5.2 gm. per 100 c.c., albumin 2.92 gm. and globulin 2.28 gm., with calculated osmotic pressure 200 mm. H_2O. The non-protein nitrogen of the plasma was 65.6 mg. per 100 c.c. The Hinton test was positive. The Takata-Ara test was negative. *Edema fluid* from the thigh contained total protein 1.50 gm. per 100 c.c., albumin 1.10 gm. and globulin 0.40 gm.

A 7-foot roentgenogram of the heart confirmed the clinical measurements (figure 4). The electrocardiogram was interpreted as within normal limits except for tachycardia. Special circulatory studies showed the venous pressure in the femoral and cubital veins to be 27 cm. H_2O; the circulation time 15.5 seconds; the femoral arteriovenous oxygen difference 0.75 volumes per cent; and the brachial arteriovenous oxygen difference 1.39 volumes per cent. The vital capacity was 2,500 c.c.

While this patient obviously was suffering from severe circulatory failure with rapid blood flow, he was made fairly comfortable with small doses of morphia. It

was thought safe to withhold therapy until a control period had elapsed. There was subjective relief, but there were no changes in the edema or other signs of circulatory failure. On the third day the venous pressure had risen to 32 cm. H_2O. It was then decided to give vitamin B_1, but before it could be administered the patient suddenly went into circulatory collapse, from which he died.

Postmortem examination revealed marked anasarca and mild jaundice of all tissues. The heart weighed 520 gm. The right auricle and ventricle showed marked dilatation and moderate hypertrophy; the left auricle and ventricle were normal. Except for the aortic cusps, at the bases of which were minimal atheromatous thickenings, all valve cusps were thin, membranous and translucent. There was no evidence of rheumatic or luetic endocarditis. The coronary arteries, the epicardium and the pericardium were normal. The aorta showed minimal atheromatous change ½ cm. above the aortic valve, but otherwise was perfectly normal.

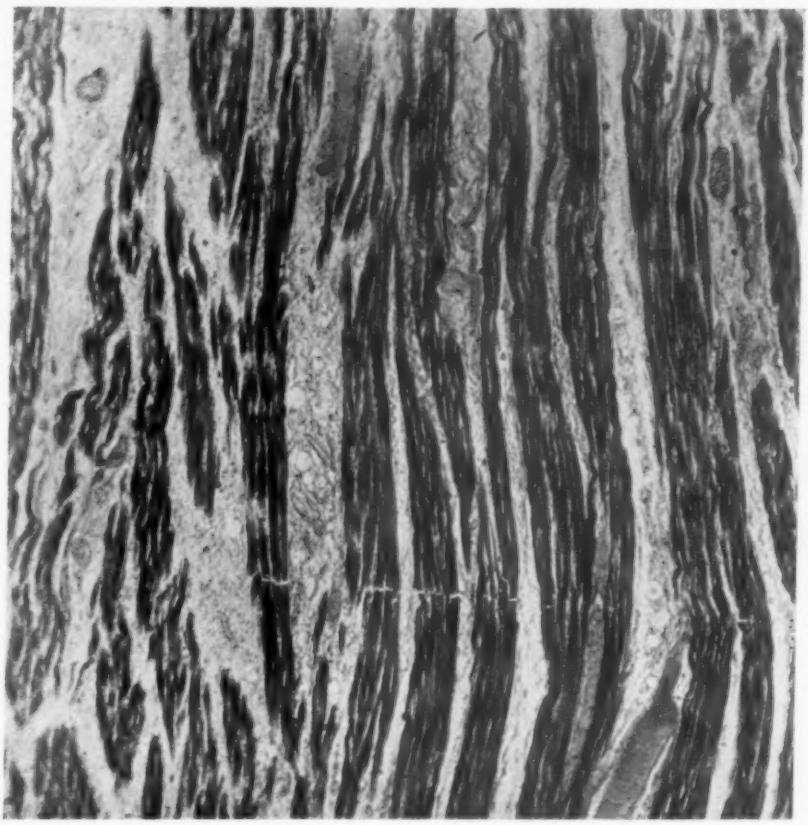

FIG. 7. Separation of the muscle fibers by edematous collagen in Case 1.

The right lung weighed 1,300 gm. and the left 1,080 gm. The pleural surfaces were smooth and glistening, but purple in hue. There were slight depressed scars at each apex. The crepitance was markedly decreased, giving the lungs a "meaty" consistency. The cut surfaces were uniformly purplish-red throughout all lobes of both lungs. There was an extreme degree of edema and congestion, and large quantities of serosanguineous fluid could be easily expressed. In the base of the right lower lobe was one small area of minimal bronchopneumonic consolidation.

The liver weighed 2,480 gm. It was firm, the surface smooth, its capsule thin and of normal translucence. Its cut surface showed a marked "nutmeg" appearance. The kidneys, spleen and other abdominal viscera were markedly congested.

The brain weighed 1,560 gm. There was atrophy of both frontal lobes, most pronounced in the pre- and post-central gyri. There were several very small petechial hemorrhages in Ammon's horn. The spinal cord and peripheral nerves were normal in appearance. The rest of the gross examination was normal.

Microscopy revealed these additional findings: The right ventricle showed marked "edema" of the intermyocardial connective tissue, with separation of the muscle fibers. There was also "intracellular edema" of the myocardium (figures 5, 6, and 7). The left ventricle showed marked increase in the collagenous connective tissue of the epicardium. There was an increase in the interstitial tissue, especially that lying immediately beneath the epicardium. This connective tissue was extremely "edematous," causing separation of the myocardial cells.

The lungs showed marked dilatation and congestion of the capillaries of the alveolar walls. The alveoli contained many large macrophages filled with brown pigment, many extravasated erythrocytes and granular débris. In one area numerous polymorphonuclear leukocytes were present.

The liver showed extreme fatty degeneration. Many cells, especially in the centers of the lobules, were degenerated. There was no increase in connective tissue. No "alcoholic" hyaline was seen. The brain showed widespread perivascular hemorrhages and degenerative changes in numerous pyramidal cells.

Case 2. *Congestive failure of the circulation, polyneuritis, Korsakoff's psychosis; improvement on vitamin* B_1. W. E., an unemployed painter, aged 50 years, was disoriented and confused and gave an unreliable history. He admitted taking one pint of pure alcohol daily for years and stated that he rarely ate anything. He was brought in by welfare workers from a cellar where he had been lying for weeks, unable to move. He had no complaints.

Physical examination revealed an extremely weak, poorly nourished man with diffuse edema which involved the sternum and face. He lay flat in bed in no apparent distress. The skin of the face showed marked acne rosacea with crusted pustular lesions. The skin of the extremities was dry, scaly and very warm. There was a pustular conjunctivitis and a small white ulcerous plaque on the right cornea. The pupils were quite small and reacted sluggishly to light. The tongue was smooth on the edges. There was moderate engorgement of the veins of the neck. The heart was percussed 11 cm. to the left and 6 cm. to the right of the midsternal line. The sounds were of poor quality but there were no murmurs. The heart rate was 90 per minute and the rhythm was regular. The arterial pressure was 105 mm. Hg systolic and 75 diastolic. Sounds were audible over the carotid, femoral and brachial arteries. The lungs were resonant, but moist râles were heard over the lower third of both lungs posteriorly. In the abdomen the liver edge was felt 1 cm. below the right costal margin. There was bilateral wrist- and foot-drop. The biceps and triceps jerks were greatly diminished and the knee and ankle jerks were not obtainable. There was marked muscle and nerve tenderness in the legs. Sensory examination was unsatisfactory, but there was apparently hypesthesia of the lower legs. Temperature was 99° F. Respirations 25 per minute. Weight 158 pounds.

Laboratory studies: *Urine,* acid, specific gravity 1.012, albumin 2 plus, sugar 0, bile 0, acetone 0, diacetic acid 0, pyruvic acid 0; sediment, many leukocytes and hyaline casts. *Blood,* hemoglobin 74 per cent, erythrocytes 3,200,000 per cu. mm., leukocytes 9,150, neutrophiles 78 per cent. The fasting blood sugar was 144.5 mg. per 100 c.c. and the non-protein nitrogen 98 mg. The total protein content of the plasma was 5.3 gm. per 100 c.c., albumin 3.0 gm., globulin 2.3 gm., with calculated osmotic pressure 207 mm. H_2O. The icterus index was 10. The Hinton test was negative. The Takata-

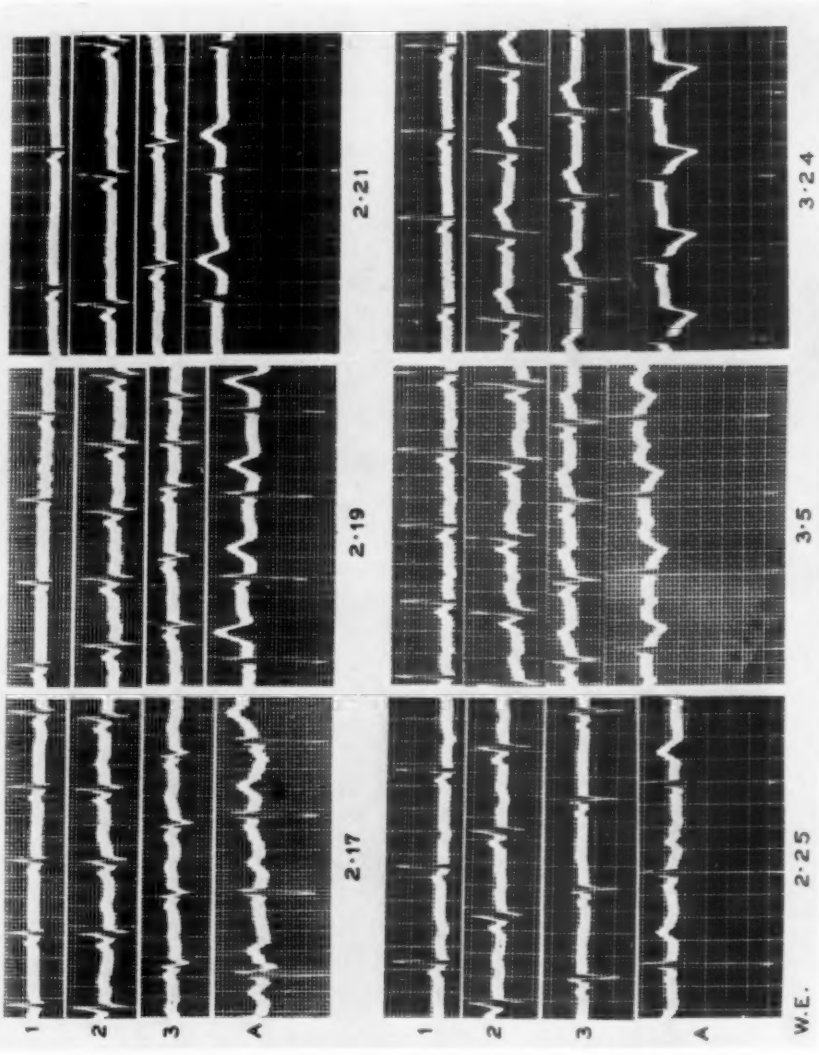

FIG. 8. Electrocardiograms in Case 2. Note changes in amplitude and in T-waves.

Ara test was positive. The bisulphite binding substances in the blood were 9.9 mg. per 100 c.c. (as pyruvic acid). *Edema fluid* from the arms showed a total protein content of 1.2 gm. per 100 c.c., albumin 0.66 gm., globulin 0.55 gm. *Lumbar puncture* revealed a spinal fluid pressure of 200 mm. H_2O, normal dynamics and a normal fluid.

Special circulatory studies showed vital capacity 1,700 c.c., venous pressure 17 cm. H_2O, circulation time 11 seconds and femoral arteriovenous oxygen difference 1.84 volumes per cent. The electrocardiogram (figure 8) showed low voltage (7 mv.), abnormal T-waves and prolonged Q–T interval (K equals 0.47), interpreted as myocardial disease. The 7-foot roentgenogram confirmed the enlargement of the heart found clinically (figure 9).

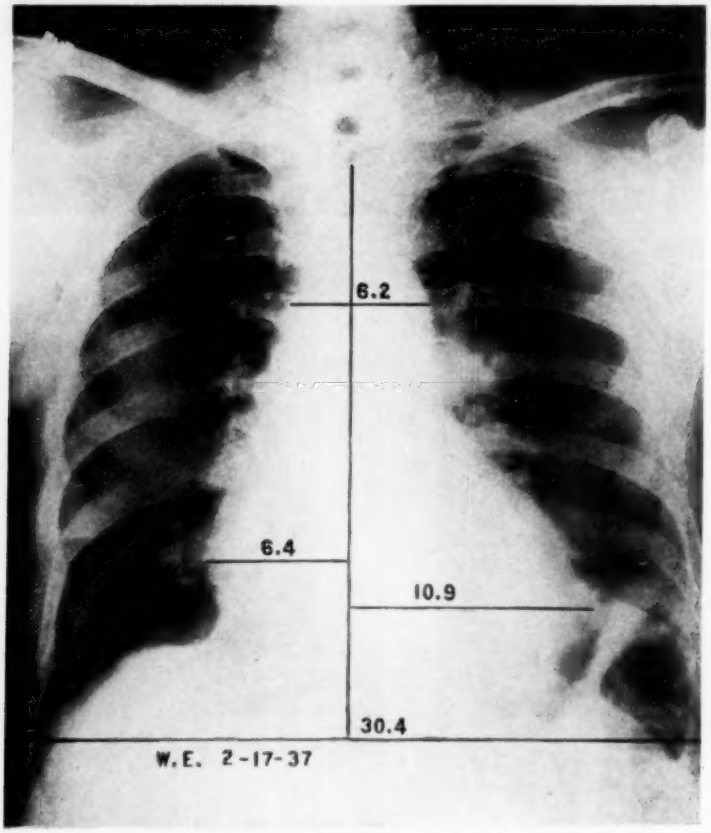

FIG. 9. The cardiac shadow in Case 2 before treatment.

The patient was placed on a vitamin-free diet, fluids ad lib., no other therapy. His course is graphically shown in chart 1. On the second day it was found that he had retention of urine, necessitating constant drainage. On the fourth day he lapsed into coma and appeared moribund. There had been no essential change in any aspect of the circulation or blood chemistry. It was decided not to delay vitamin therapy. Accordingly, 30 mg. of synthetic crystalline vitamin B_1 were administered intravenously. At that time the patient was in deep coma, had Kussmaul breathing, and extremely small pupils which did not react to light. One hour and a half after the injection there was a most remarkable change. The patient aroused, asked for water,

then took a large bowl of boiled milk and crackers. The breathing became normal, the pupils were dilated and reacted normally to light and on accommodation. Vitamin B_1 was continued, both intravenously and subcutaneously, in large doses. In this case it seemed to have been life saving.

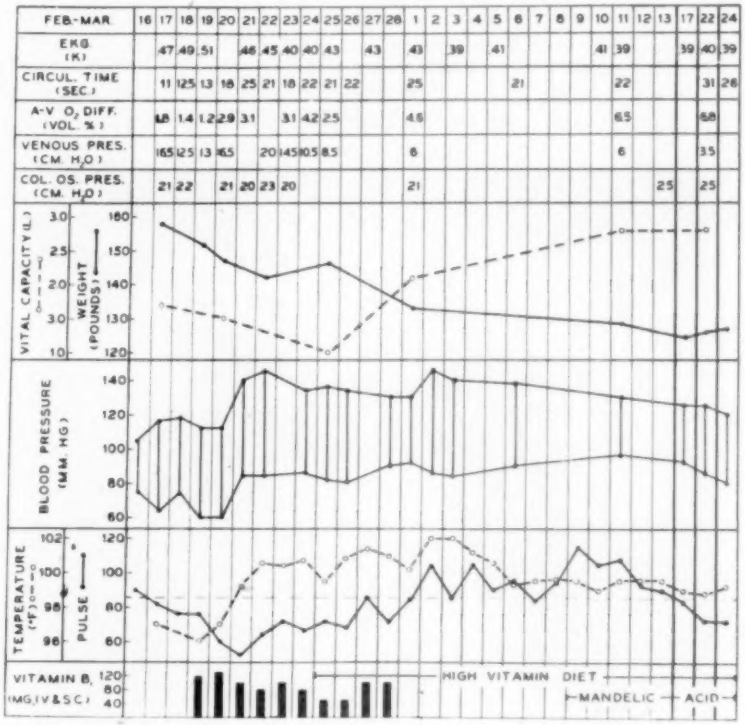

CHART 1. The clinical course in Case 2.

The next day the heart rate was 60 per minute, the circulation time 18 seconds, and the femoral arteriovenous oxygen difference 2.9 volumes per cent. The arterial pressure, venous pressure and colloid osmotic pressure of the blood were unchanged. On the second day after vitamin B_1 therapy was instituted the heart rate was as low as 52, the arterial pressure was 140 mm. Hg systolic and 84 diastolic and the electrocardiogram (figure 8) showed increased voltage (10 mv.). The circulation time was 25 seconds and the arteriovenous oxygen difference 3.1 volumes per cent. The slowing of the circulation shown by these measurements was all the more remarkable in view of the fact that the patient now had a fever due to cystitis and also, probably, to bronchopneumonia. The latter diagnosis could not be established because, while there were signs of dullness, bronchovesicular breathing and moist râles over the hilar regions of both lungs posteriorly, these signs might have been due simply to increased pulmonary congestion resulting from compensation of the right ventricle out of proportion to the left. We have observed these signs without fever in similar cases, and in this case the fever continued after the lungs had cleared and until the urinary infection was brought under control. The vital capacity decreased during this period, but later returned toward normal. On the third day of vitamin therapy the non-protein nitrogen, the bisulphite binding substances in the blood and the Q–T interval of the electrocardiogram were within normal limits. There was still no

change in the venous pressure or the colloid osmotic pressure of the blood. Clinically, in spite of the fever, the extremities were now cool, the sounds had disappeared over the brachial arteries and were barely audible over the femoral arteries. There was less edema, especially of the upper part of the body.

This patient's course was complicated by a prolonged febrile episode, due to the stubborn cystitis which required forcing of fluids. Nevertheless, he responded well to the vitamin therapy. On the sixth day of this treatment the edema had greatly decreased and the venous pressure was normal. The colloid osmotic pressure of the blood was still unchanged. He was then placed on a high vitamin diet, and after four days the parenteral vitamin B_1 was discontinued.

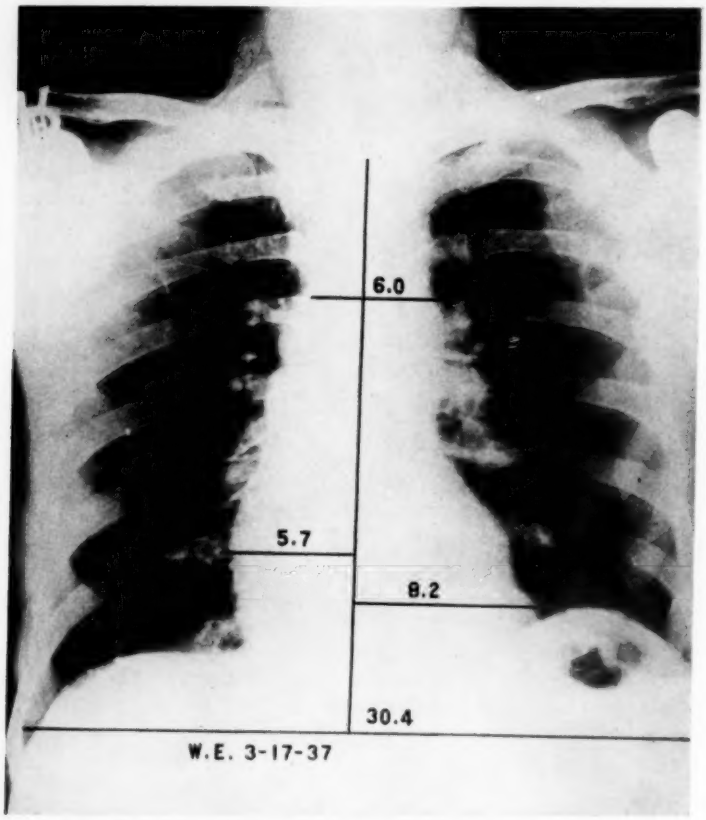

FIG. 10. The cardiac shadow in Case 2 after treatment.

Convalescence was steady and complete. The patient regained voluntary control of his bladder and the cystitis was relieved by mandelic acid. One month after admission a 7-foot roentgenogram showed that the heart had decreased to normal size (figure 10). Except for a flat T-wave in the first lead, the electrocardiogram was normal (figure 8). The vital capacity was 2,800 c.c. The patient had lost a total of 34 pounds. In the fifth week the knee jerks returned, and the strength was greatly improved. During the sixth week the patient was up and about the ward. He began to gain weight without edema. The protein content of the blood plasma was normal. Mentally, although greatly improved, he was still defective. His memory was poor and he confabulated. Consequently, at the end of the sixth week he was committed to a sanatorium for chronic care.

Case 3. *Congestive failure of the circulation and polyneuritis; improvement after vitamin B_1 therapy.* J. S., a laborer, aged 36 years, had drunk ½ to 1 pint of whisky and many glasses of beer daily for 15 years. His food intake had been scanty, and particularly deficient in vitamins. He complained of palpitation on exertion for three months, of dependent edema for one month, which had involved the scrotum for one day, and of dyspnea on exertion for three weeks.

The family history was non-contributory. The past history was negative except for one previous hospital admission two years before, for alcoholic gastritis.

Physical examination revealed a well-nourished, nervous man fairly comfortable in bed, with marked edema of the scrotum and slight edema over the shins and sacrum. The color was quite florid and the skin was warm and moist. The heart was percussed 12 cm. to the left and 5 cm. to the right of the midsternal line. The sounds were tic-tac in quality and there was a short blowing systolic murmur at the apex. The heart

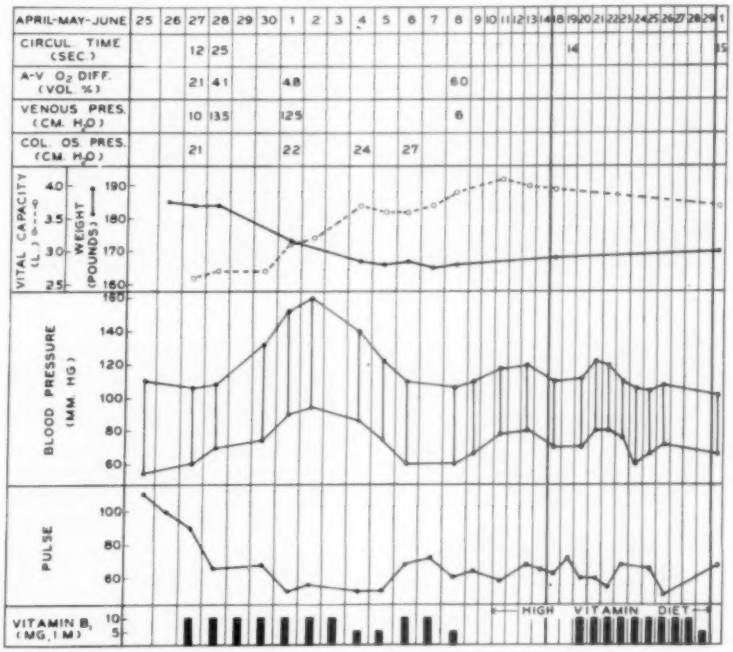

CHART 2. The clinical course in Case 3. Note the temporary elevation of the arterial pressure following the first, but not the second course of crystalline vitamin B_1.

rate was 110 per minute and the rhythm was regular. The arterial pressure was 110 mm. Hg systolic and 54 diastolic. Systolic sounds were audible over the carotid, femoral and brachial arteries. The lungs were resonant and clear except for moist râles at the left base posteriorly. The abdomen was negative. The knee jerks and ankle jerks were not obtainable. Temperature 99.2° F. Respirations 24 per minute. Weight 185 pounds.

Laboratory studies: *Urine,* alkaline, specific gravity 1.020, albumin, sugar, bile and sediment negative. *Blood,* hemoglobin 90 per cent, erythrocytes 4,260,000 per cu. mm., leukocytes 4,700, neutrophiles 61 per cent. The non-protein nitrogen was 32 mg. per 100 c.c. The Kahn test was negative. The Takata-Ara test was negative. The *basal metabolic rate* was plus 4 per cent.

This patient was not seriously ill on admission; indeed, aside from the swelling of the scrotum there was no striking evidence of circulatory failure. He was placed on a low vitamin diet and all medication was withheld. On the third day there was no change clinically. Studies on that day showed the following: weight 185 pounds, arterial pressure 106 mm. Hg systolic and 60 diastolic, heart rate 90 per minute, vital

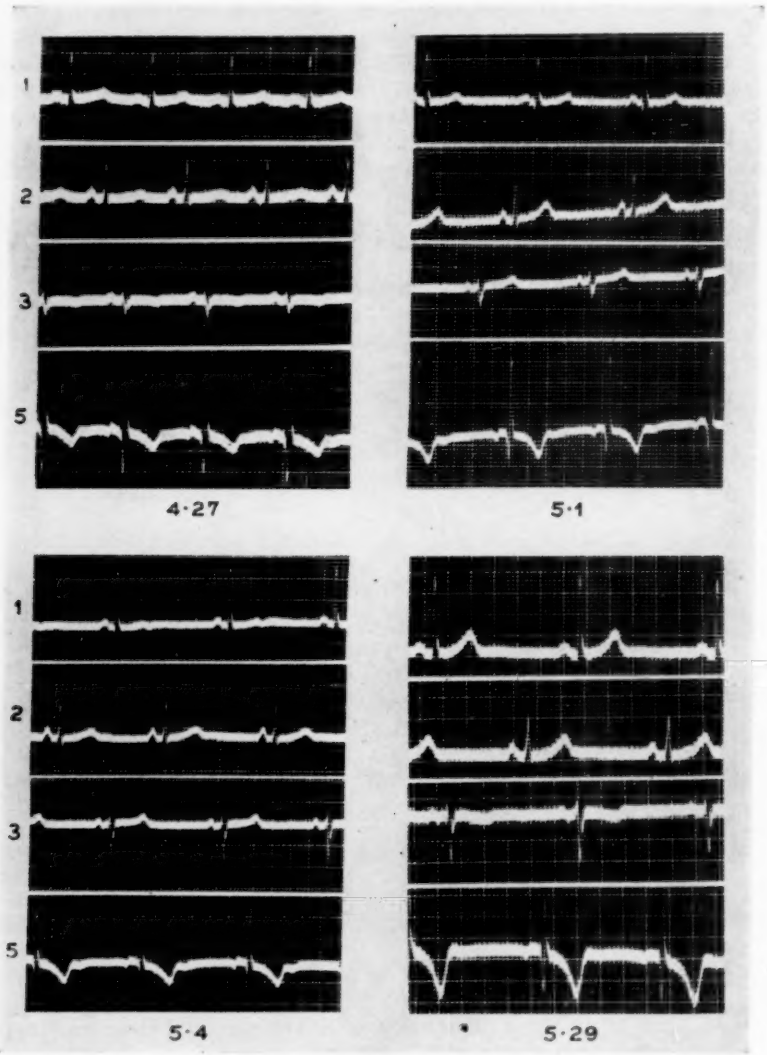

FIG. 11. Electrocardiograms in Case 3. Note changes in T-waves.

capacity 2,600 c.c., venous pressure 10 cm. H_2O, circulation time 12 seconds, the femoral arteriovenous oxygen difference 2.08 volumes per cent. The total protein content of the blood plasma was 5.07 gm. per 100 c.c., the albumin 3.28 gm. and globulin 1.79 gm., with a calculated osmotic pressure of 210 mm. H_2O. The electrocardiogram showed no abnormality (figure 11). A 7-foot roentgenogram of the heart showed the heart enlarged as observed clinically.

After these observations vitamin B_1 was given intramuscularly in 5 mg. doses twice daily. The clinical course and circulatory measurements are shown in chart 2. The striking changes one day after the vitamin were the slowing of the heart rate to 66 per minute and of the circulation time to 25 seconds, and the increase in the femoral arteriovenous oxygen difference to 4.09 volumes per cent. The venous pressure had risen slightly to 13.5 cm. H_2O. There was also a striking change in the clinical appearance of the patient. His face, previously bright pink, was now definitely cyanotic, the hands and feet were quite cool; only the faintest sound could be heard over the carotid artery and no sound over the femoral or brachial arteries.

Four days after vitamin therapy was instituted the heart rate was 52 per minute, the blood pressure had risen to 152 mm. Hg systolic and 90 diastolic, the vital capacity had increased to 3,100 c.c. and the patient had lost 12 pounds of edema fluid, in spite of the fact that there was no essential change in the venous pressure or colloid osmotic pressure of the blood. Marked clinical improvement coincided with these circulatory changes. In 10 days following the vitamin therapy the patient had lost 20 pounds of weight, and the vital capacity, the blood pressure, heart rate, venous pressure and femoral arteriovenous oxygen difference had returned to normal. An interesting change in the electrocardiogram at this time was the inversion of the T-wave in Lead I, which subsequently reverted to normal (figure 11).

At the beginning of the third week the parenteral injection of vitamin B_1 was stopped, and a high vitamin diet started. The knee jerks returned in the middle of the fourth week. At the end of the fourth week a second course of parenteral vitamin B_1 was given, exactly as before, with no effect on any aspect of the circulation.

The patient was discharged well at the end of the sixth week.

Case 4. *Congestive failure of the circulation, the only manifestation of vitamin deficiency; when treated with digitalis and diuretics showed little improvement, on vitamin B_1 striking improvement.* J. F., an unemployed waiter, aged 60 years, for four years had spent but 25 cents a day on food, which was grossly inadequate in vitamins. He had taken an average of 10 glasses of ale and 2 glasses of whisky daily for one year. He complained of cough for six months, dyspnea on exertion for one month, orthopnea for two weeks, increasing dependent edema for 10 days and swelling of the abdomen for one week.

The family history showed that one brother died of alcoholism. The past history was non-contributory.

Physical examination showed an elderly, apparently well-nourished man, with severe orthopnea, and extreme dyspnea on the slightest exertion. His color was cyanotic, but at times only slightly so. There was marked dependent edema up to the sternum. The skin of the face and extremities was warm and dry. There was moderate engorgement of the veins of the neck. The heart was percussed 11 cm. to the left and 5 cm. to the right of the midsternal line. There was a rough blowing systolic murmur heard over the entire precordium, loudest at the apex. The heart rate was 120 per minute and the rhythm was regular except for occasional extrasystoles. The arterial pressure was 140 mm. Hg systolic and 80 diastolic. Loud sounds were heard over the carotid and femoral arteries. Percussion of the chest revealed diminished resonance posteriorly at both lung bases, where moist râles were heard. The abdomen was tensely distended, with shifting dullness in the flanks and a palpable fluid wave. No organs were felt. The neurological examination was negative. Temperature 98° F. Respirations 30 per minute. Weight 184 pounds.

Laboratory studies: *Urine*, acid, specific gravity 1.015, albumin 0, sugar 0, bile 0, acetone 2 plus, diacetic acid 0, pyruvic acid 0; sediment, many leukocytes. *Blood*, hemoglobin 85 per cent, erythrocytes 3,700,000 per cu. mm., leukocytes 12,400, neutrophiles 85 per cent. The non-protein nitrogen was 28 mg. per 100 c.c., the fasting

blood sugar 94.1 mg. per 100 c.c. and the carbon dioxide capacity 79.2 volumes per cent. The total protein content of the plasma was 4.8 gm. per 100 c.c., albumin 2.57 gm., globulin 2.23 gm., calculated osmotic pressure 178 mm. H_2O. Icterus index 20. The Hinton test was negative. The Takata-Ara test was positive. Bisulphite binding substances in the blood (calculated as pyruvic acid) were 12.89 mg. per 100 c.c. *Edema fluid* from the thighs showed a total protein content of 0.34 gm. per 100 c.c.,

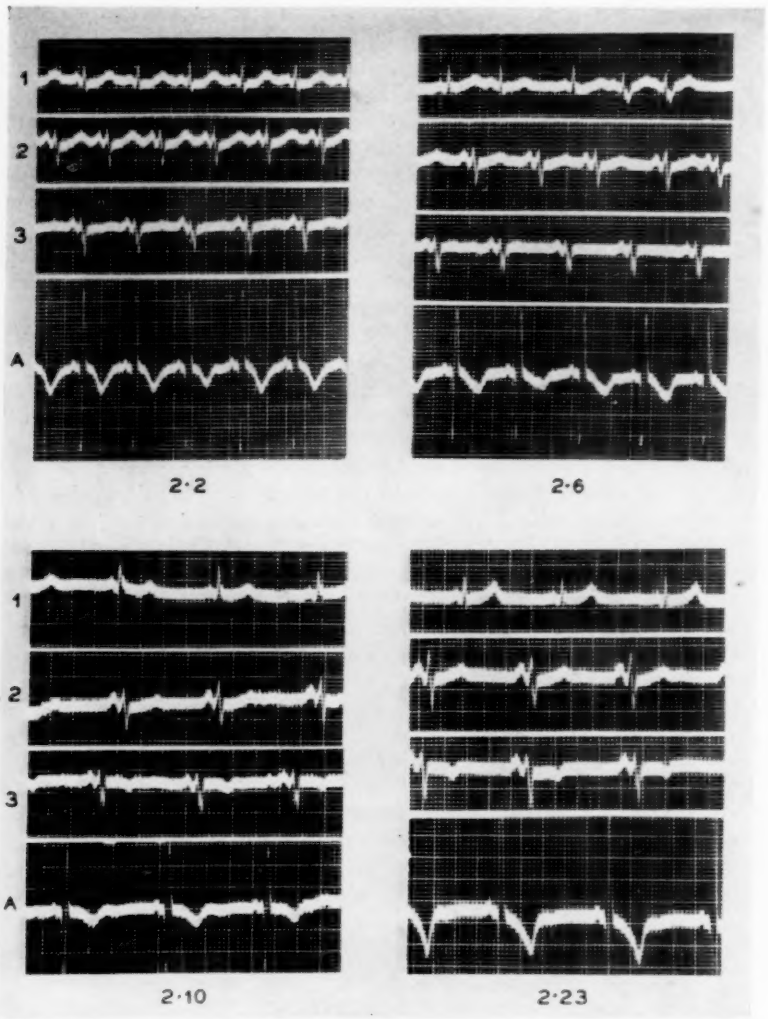

FIG. 12. Electrocardiograms in Case 4. Note changes in rate and in T-waves.

albumin 0.095 gm., globulin 0.234 gm. The vital capacity was 1000 c.c. and the venous pressure 17 cm. H_2O. The electrocardiogram showed tachycardia, low voltage (6 mv.) and prolonged Q–T interval (K equals 0.52), suggesting myocardial disease (figure 12).

Because of the patient's precarious condition, his age, and the finding of a loud systolic murmur at the apex of the heart, it was deemed wise to treat him at once with

the standard cardiac drugs but to withhold vitamin therapy. Accordingly, he was put on a Karell diet (boiled milk), was digitalized rapidly and was given ammonium chloride, Aminophyllin and Salyrgan (two doses of 2 c.c. intravenously) as diuretics. Morphia was used as a sedative with marked subjective relief. There was a fall in pulse rate but no diuresis—the daily output ranged from 700 to 1,100 c.c. This regime was maintained for four days, and on the fifth day the following observations were made: arterial pressure 145 mm. Hg systolic and 82 diastolic, heart rate 80 per minute, venous pressure 15 cm. H_2O, circulation time 13 seconds, femoral arteriovenous oxygen difference 3.66 volumes per cent. The vital capacity was 1,250 c.c. The

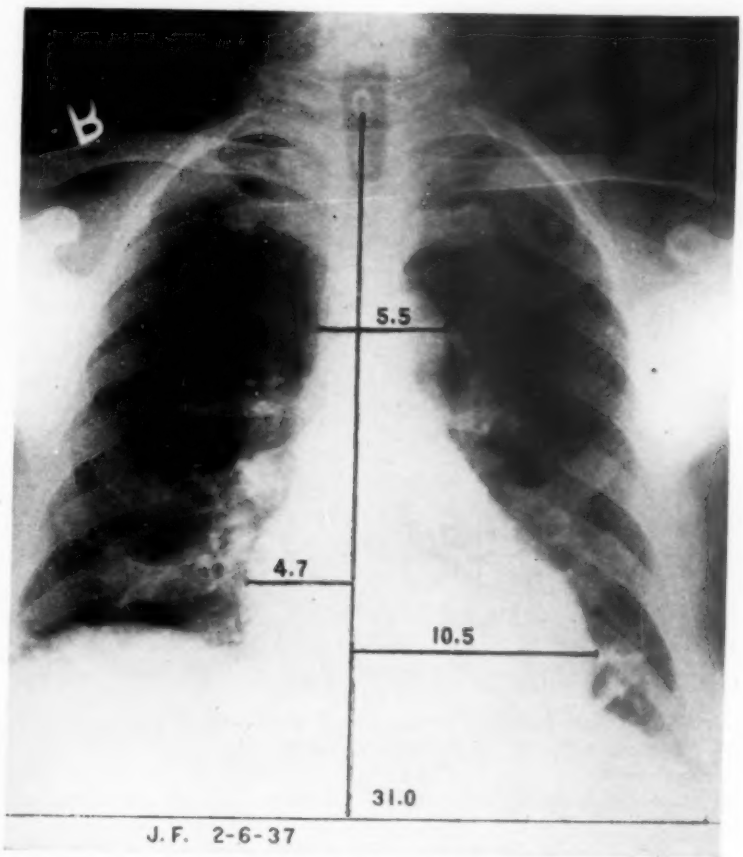

FIG. 13. The cardiac shadow in Case 4 before vitamin B_1 treatment.

total protein content of the blood plasma had risen to 5.38 gm. per 100 c.c., albumin 2.67 gm., globulin 2.71 gm., producing a calculated osmotic pressure of 200 mm. H_2O. This was evidence of hemoconcentration, as the values two days later had fallen to and below their previous levels. A 7-foot roentgenogram showed the heart still enlarged to the left and right (figure 13).

On the fifth day *all medication* was omitted, and the deficient diet continued unchanged. Synthetic crystalline vitamin B_1 was given in 10 mg. doses subcutaneously five times a day. The next day the urine output was 1,500 c.c. and rose progressively to reach a peak of 4,800 c.c. four days after the vitamin was started.

The clinical course and circulatory measurements are shown in chart 3. Of particular interest on the second day after vitamin therapy were the elevation of the blood pressure to 160 mm. Hg systolic and 90 diastolic, the slowing of the heart rate to 60 per minute, the increase in the circulation time to 25 seconds and the increase in the arteriovenous oxygen difference to 4.8 volumes per cent. The venous pres-

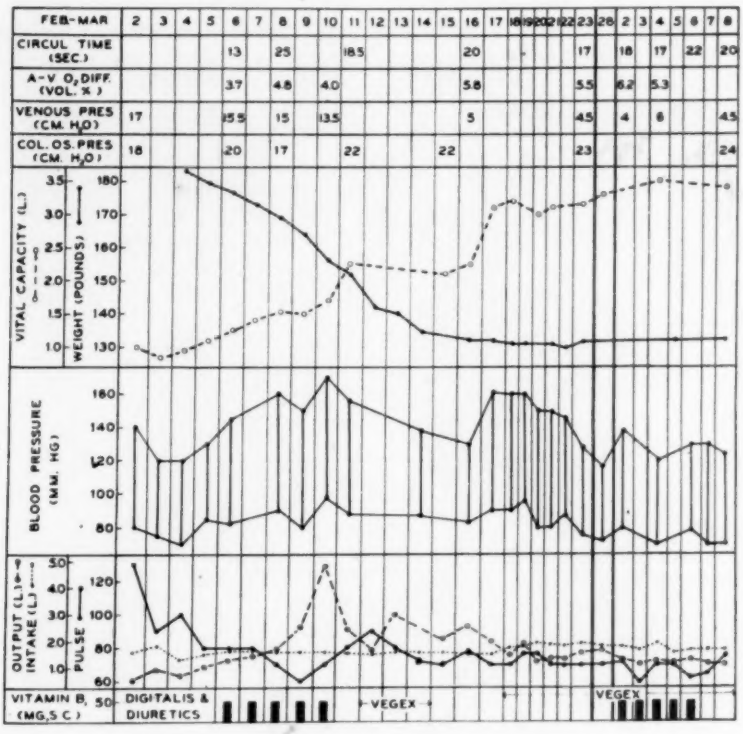

CHART 3. The clinical course in Case 4.

sure and colloid osmotic pressure of the blood were still essentially unchanged, but subsequently became normal, as did the blood pressure, the heart rate and other aspects of the circulation.

The clinical improvement coincident with these changes was dramatic. Except for a brief febrile episode with signs of bronchopneumonia on the sixth day after vitamin treatment, the course was one of steady improvement. The patient lost 51 pounds of weight in 12 days. He was then seen to be a thin-faced, frail individual, rather than the well-nourished man he had seemed on admission. The cyanosis, the orthopnea and the dyspnea on exertion disappeared, while the vital capacity rose to a normal value.

On the eleventh day a high vitamin diet was begun. In the fifth week, when all the circulatory measurements had been normal for one week, the same course of vitamin B_1 was repeated with no effect whatever. The patient was discharged well at the end of the fifth week. The 7-foot roentgenogram (figure 14) showed that the heart had returned to normal size.

Case 5. *Congestive failure of the circulation, cardiac asthma, polyneuritis, mild psychosis; improvement on high vitamin diet and continuous high alcohol intake.*

O. O., a corsetière, aged 37 years, had consumed one pint of whisky daily for seven years. Her diet was meager, rarely contained vegetables or meat, and consisted principally of coffee, tea, and sandwiches of white bread.

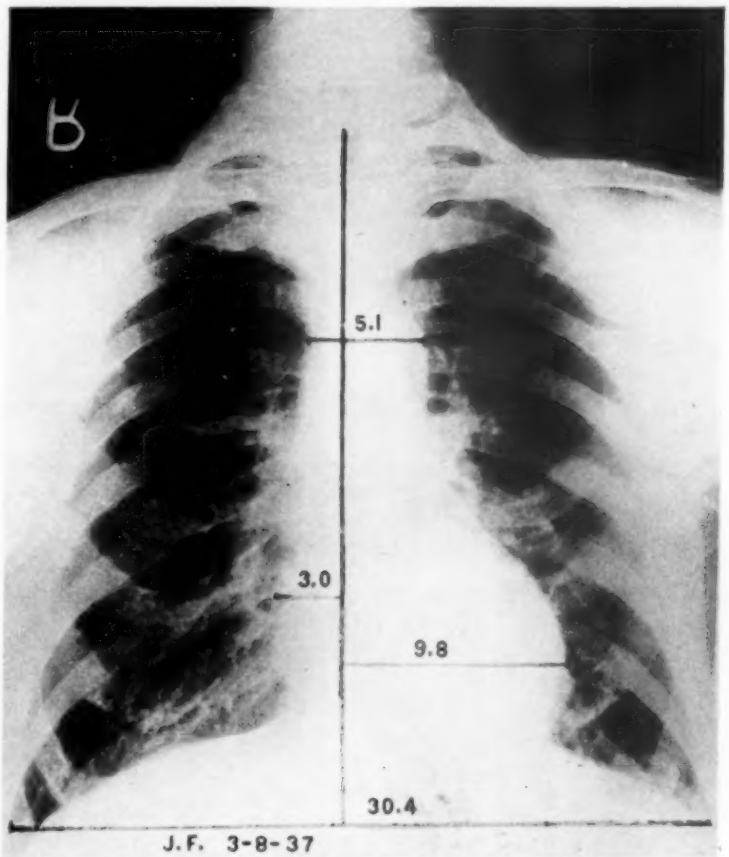

FIG. 14. The cardiac shadow in Case 4 after improvement.

She complained of intermittent weakness and numbness in the feet for six years, increasing and progressing upward to involve the legs and finally the hands for three months. For two years she had had palpitation and dyspnea on exertion, and for one year swelling of the ankles. She also complained of orthopnea for three weeks, and nocturnal attacks of paroxysmal dyspnea for two weeks.

The family history revealed that the paternal relatives were alcoholics; otherwise it was non-contributory. The past history was non-contributory.

Physical examination showed a well-nourished, mildly psychotic, apprehensive, orthopneic woman with marked edema of the legs. The skin was thick, warm and moist. The veins of the neck were distended. The heart was percussed 11 cm. to the left and 5 cm. to the right of the midsternal line. There was a gallop and a short blowing systolic murmur at the apex. The heart rate was 120 per minute and the rhythm was regular. The arterial pressure was 110 mm. Hg systolic and 70 diastolic. The carotid and peripheral arteries showed increased pulsations. The lungs were resonant and clear. In the abdomen the liver edge was felt just below the right

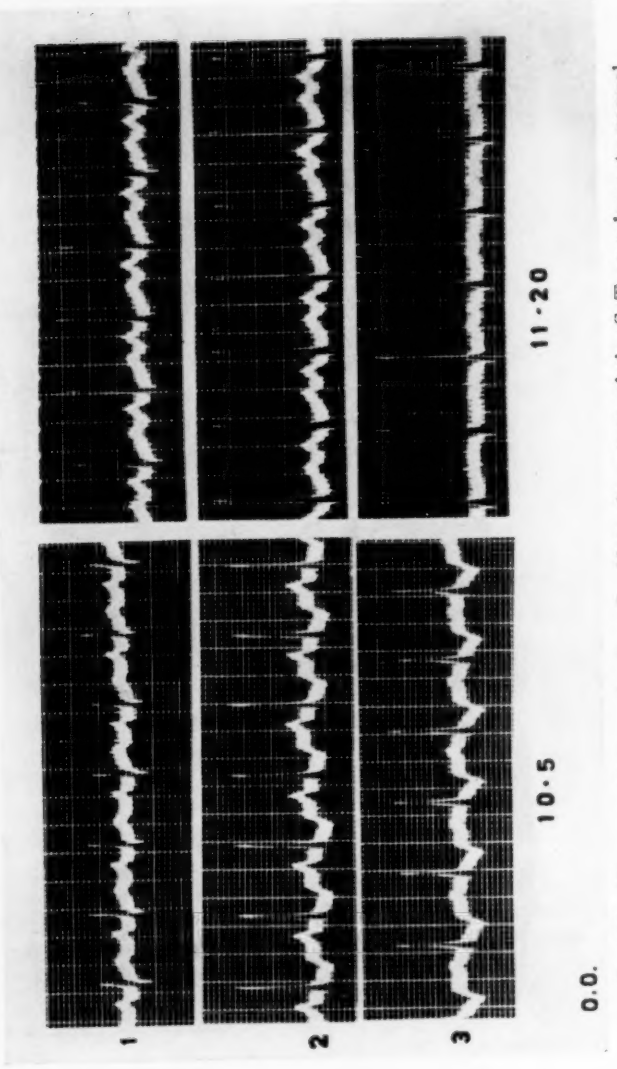

FIG. 15. Electrocardiogram in Case 5. Note the return of the S–T complexes to normal following the continued administration of oral vitamin B concentrate and alcohol.

costal margin. There was bilateral toe drop, absent knee and ankle jerks, and absent vibration sense below the knees. Temperature 99° F. Respirations 25 per minute. Weight 167 pounds.

Laboratory studies: *Urine*, acid, specific gravity 1.019, albumin 0, sugar 0; sediment, many leukocytes. *Blood*, hemoglobin 82 per cent, erythrocytes 4,230,000 per cu. mm., leukocytes 9,300, neutrophiles 76 per cent. The non-protein nitrogen was 60 mg. per 100 c.c. of blood. The total protein content of the plasma was 6.5 gm. per 100 c.c., albumin 3.25 gm., globulin 3.25 gm., with calculated osmotic pressure 264 mm. H_2O. The Kahn test was negative. Roentgenogram confirmed the enlargement of the heart and showed congestion of the lung fields. Electrocardiogram (figure 15) showed tachycardia, and abnormal T–waves suggesting myocardial disease.

For five days the patient was kept on a house diet with no essential change in her condition. She was then placed on a high vitamin diet, supplemented by oral yeast extracts and intramuscular liver extract. In addition she was given one pint of whisky a day. On this regime she improved rapidly. The nocturnal dyspnea, the edema and palpitation disappeared. Within two weeks the heart rate had decreased to 90 and the gallop had disappeared. After six weeks the electrocardiogram was normal (figure 15). There was slower but steady improvement in the neurological and mental symptoms. When discharged from the hospital, four months after entrance, she was able to walk satisfactorily and the psychosis had cleared, but some abnormal neurological signs still persisted in the legs. She had continued to receive one pint of whisky daily until discharge.

Case 6. *Acute cardiac dilatation and congestive failure associated with polyneuritis; improvement after rest, digitalis, good diet and oral vitamin "B" extract.* W. F., a laborer, aged 32 years, had consumed ½ pint of pure alcohol daily for five years. He had eaten little food because of an extremely poor appetite. He complained of increasing dyspnea on exertion for two years, increasing swelling of the legs for one year, and difficulty in walking associated with numbness of the feet and hands for six months. The family history and the past history were non-contributory.

Physical examination revealed a small but well-nourished man, comfortable, flat in bed with marked edema of the lower legs. The skin was dry, warm and of good color. The veins of the neck were distended and showed marked pulsations. The heart was percussed 11 cm. to the left and 6 cm. to the right of the midsternal line. The precordium was heaving rapidly. A marked gallop was heard near the apex, where there were also loud, rough systolic and diastolic murmurs. Over the aortic area blowing systolic and diastolic murmurs were heard. The heart rate was 100 per minute and the rhythm was regular. The arterial pressure was 130 mm. Hg systolic and 60 diastolic. There were marked pulsations of all peripheral arteries, over which loud "pistol" sounds were audible. The lung bases were dull posteriorly. In the abdomen the liver was palpated 4 cm. below the right costal margin. The knee and ankle jerks were not obtainable. Temperature 100° F. Respirations 20 per minute. Weight 113 pounds.

Laboratory studies: *Urine*, first specimen acid, specific gravity 1.036, albumin 0, sugar 3 plus, bile positive, acetone 0, diacetic acid 0; sediment, negative. Later specimens negative. *Blood*, hemoglobin 78 per cent, erythrocytes 4,220,000 per cu. mm., leukocytes 9,800, neutrophiles 65 per cent. The non-protein nitrogen was 22 mg. per 100 c.c., the fasting blood sugar on the third day 93 mg. per 100 c.c. The total protein content of the blood plasma was 6.3 gm. per 100 c.c., albumin 3.4 gm., globulin 2.9 gm., with calculated osmotic pressure 260 mm. H_2O. The Kahn test was negative. The Takata-Ara test was negative.

A 7-foot roentgenogram of the heart on the second day showed enlargement. (Figure 16.) The electrocardiogram showed a flat T-wave in Lead I and prolonged Q–T interval (K equals 0.46), interpreted as myocardial disease.

Because of the diastolic murmurs heard on admission it was thought that the patient had organic valvular heart disease. He was digitalized rapidly and given a high vitamin diet supplemented by oral extracts of vitamin B. On the second day no diastolic murmur could be heard. The improvement was rapid. On the seventh day he was allowed out of bed. The digitalis was omitted. A 7-foot roentgenogram at the beginning of the fifth week (figure 17) showed a small heart. He was discharged well in the sixth week.

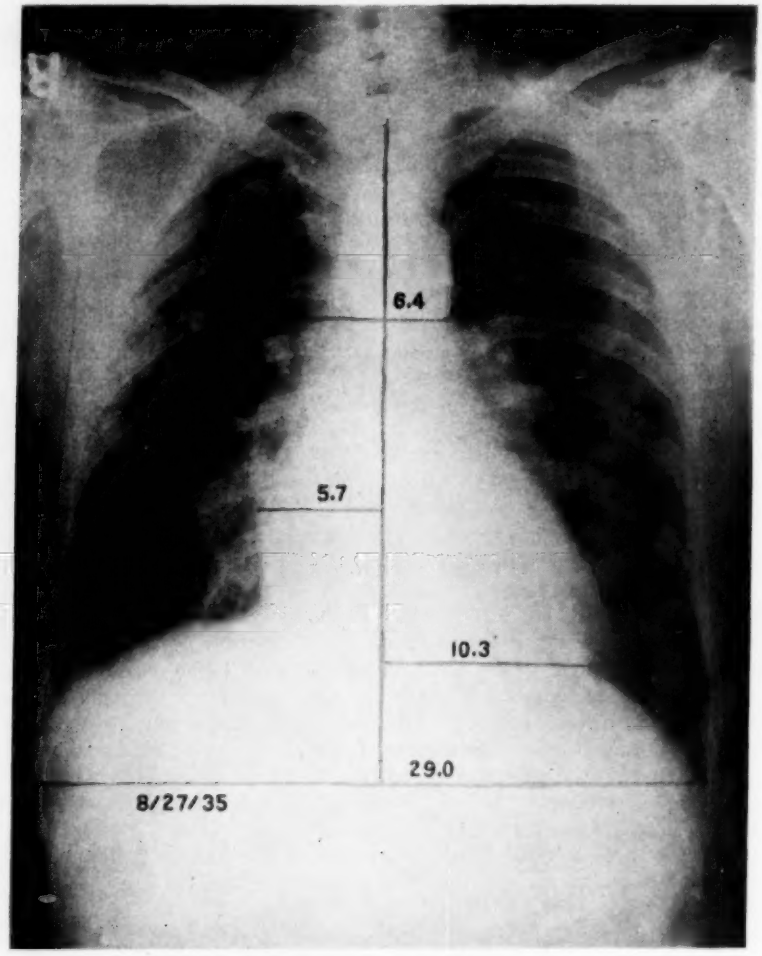

FIG. 16. The cardiac shadow in Case 6 on the first day after admission.

Case 7. *Repeated admissions for attacks of carotid sinus syncope and circulatory failure associated with polyneuritis; relief after diet and extracts rich in vitamin "B."* E. S., an unemployed odd-job man, aged 47 years, had drunk one pint to one quart of liquor daily for years. He had eaten irregularly and his diet was of poor quality. He was admitted to the hospital on three occasions with essentially the same complaints. These were dizziness and attacks of syncope, soreness of the mouth and tongue, pain, weakness and numbness in the legs, nocturnal cough, dyspnea on exertion and nocturnal attacks of paroxysmal dyspnea.

Physical examination revealed a poorly nourished man with no orthopnea or edema. The skin was pale. The mucosa of the mouth and tongue was red, with patchy ulcerated areas covered by whitish exudate. The heart was percussed 7 cm. to the left and 3 cm. to the right of the midsternal line. There was a blowing systolic murmur at the apex. The heart rate was 110 to 120 per minute, and the rhythm was regular. The arterial pressure was 115/70 to 120/90 mm. Hg. The abdomen was

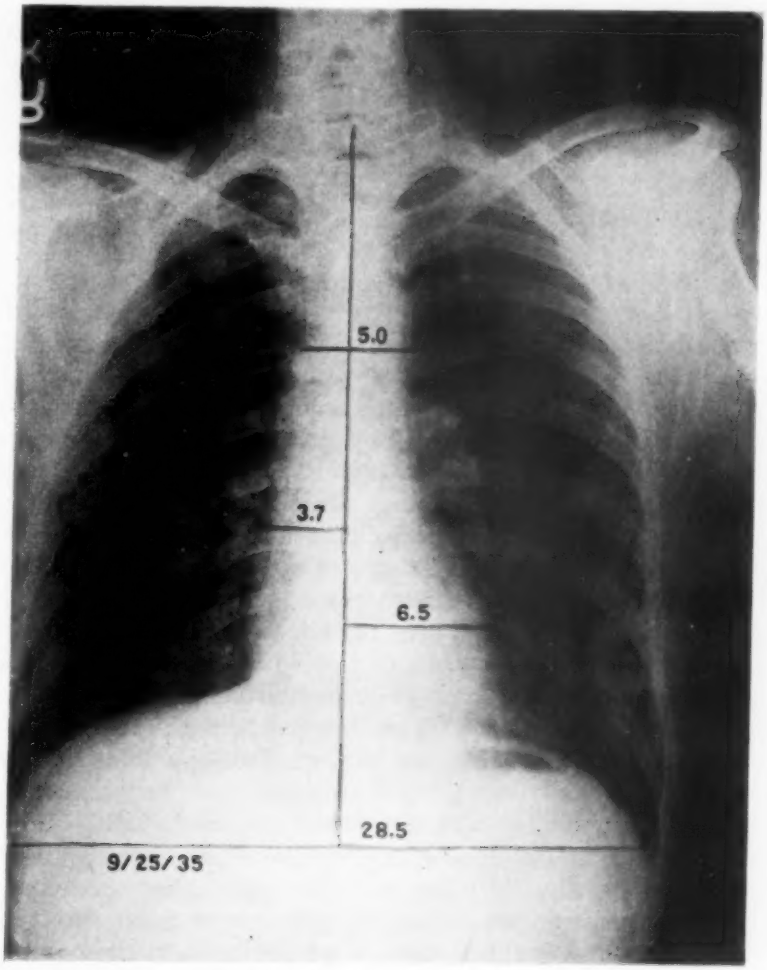

FIG. 17. The cardiac shadow in Case 6 following improvement.

negative. The ankle jerks were not obtainable and the vibration sense was absent below the knees. Temperature 99° to 100° F. Respirations 20 to 25 per minute. Weight 135 to 145 pounds.

Laboratory studies: *Urine*, acid, specific gravity 1.020, albumin, bile, sugar and sediment negative. *Blood*, hemoglobin 55 per cent, erythrocytes 4,000,000 per cu. mm., leukocytes 5,700, neutrophiles 71 per cent. The non-protein nitrogen was 30 mg. per 100 c.c. The Kahn test was negative. *Lumbar puncture* revealed normal pressure and normal spinal fluid. *Gastric analysis* showed no free acid after his-

tamine. The 7-foot roentgenogram showed no abnormality of heart or lungs. The electrocardiogram showed flattening or inversion of the T–waves in Leads I and II, interpreted as myocardial disease.

On each admission under treatment with a good rest, intramuscular liver and vitamin "B" extracts, there was complete relief of the cardiovascular symptoms within two weeks. It is of interest that with improvement the blood pressure rose from 140/104 to 200/120 mm. Hg. The improvement in the neurological symptoms was equally striking, but slower.

On the second admission it was found that even mild stimulation of the carotid sinus caused complete asystole of the heart and syncope. The patient stated that the induced attack was the same as the spontaneous spells of which he complained. Six days after vitamin therapy the dizziness had improved, and carotid sinus pressure now induced no asystole but an idioventricular rhythm with a rate of 30 per minute. Slight dizziness but no syncope accompanied the slowing. Four days later, and thereafter, stimulation of the carotid sinus induced only transient physiological slowing of the sinus rhythm and no dizziness. He was discharged improved in the third week.

Discussion

The association of cardiovascular dysfunction with nutritional deficiency suggests a possible causative interrelation between the two conditions. Furthermore, the characteristics of the cardiovascular disturbances and the frequent coexistence of nervous disorders indicate a similarity between the condition observed and oriental beriberi. It was the primary purpose of this investigation to ascertain whether the disease studied is only similar to or is actually identical with the cardiovascular disturbances occurring in beriberi.

Beriberi is considered to be primarily an avitaminosis, and the polyneuritic form of the disease has been reproduced experimentally in animals fed a diet lacking in vitamin B_1. In spite of the fact that a descriptive knowledge of this disease dates back to ancient Chinese and Japanese records, the etiology and pathogenesis are but partially clarified. The cardiac form of the disease has heretofore been studied only in the Orient. In recent years particularly, extensive investigations on "beriberi heart" have been carried out in Java by Wenckebach and Aalsmeer.[10, 11]

The Occurrence of Beriberi in the United States. As recently as 1932, Wenckebach [13] stated that "beriberi is, or is supposed to be an avitaminosis, which is met in such tropical countries only where rice is the prevailing food." Nevertheless, scattered reports are available on the occurrence of beriberi in other parts of the world, including the United States. Scott and Herrmann [14] have reported cardiac manifestations among rice workers in Louisiana. Kepler [15] has observed one and Riesman and Davidson [16] two suggestive cases with cardiac manifestations.* There are also a few reports on polyneuritis due to food deficiencies, in which the authors considered the clinical syndrome identical with beriberi. Wohl [17] described such a poly-

* Since this paper was sent in for publication, B. Sure and W. A. Jones have reported (personal communication) a study on the rôle of vitamin B_1 in cardiovascular diseases in 30 patients at the U. S. Veteran's Hospital, Fayetteville, Arkansas.

neuritic form of beriberi in a young diabetic patient who lived on an unbalanced diet.

Minot, Strauss and Cobb [3] concluded that in alcoholic polyneuritis the etiological factor is vitamin B deficiency, rather than excessive use of alcohol. Jolliffe, Colbert and Joffe [18] have demonstrated that, according to Cowgill's formula, the vitamin B (B_1) intake of alcoholic patients with polyneuritis is decreased to well within the limit required for the induction of polyneuritis in animals. Among the patients with polyneuritis and pellagra whose records are on file in the Boston City Hospital, consumption of a large amount of alcohol, usually over a prolonged period, frequently occurred. In comparing the clinical characteristics of "alcoholic pellagra" and "nonalcoholic pellagra," Spies [19] observed no difference between the two types. Our clinical experience, similarly, fails to reveal any difference between alcoholic and nonalcoholic deficiency polyneuritis and pellagra. These considerations strongly suggest that the polyneuritis and pellagra observed in both alcoholic and nonalcoholic patients with food deficiency are of similar, if not identical, etiology, and that both of these conditions bear a causative relationship to the avitaminosis.

"Beriberi Heart" as Heretofore Described. There are mainly two explanations of the pathogenesis of "beriberi heart." The older theory, advocated by early Japanese workers, is that the cardiac disease is caused by a disturbance of the function and a "degeneration" of the *vagus nerves.*[20] The frequent observation of rapid heart and the demonstration of demyelinization of the vagus nerves were offered as evidence for this theory. The histological evidence of structural changes in peripheral nerves is, however, inadequate. Some of the cases studied by us showed histological changes within the vagus centers.

Lately the vagus theory has given way to the myogenic theory. Wenckebach [13] consider the essential change in the heart to be degeneration of the muscle which "robs the heart of its means of resistance to stretching, and deadens its power of contractility." In addition there is widening of the peripheral arterioles which results in a rapid and increased volume flow to the right side of the heart. The right ventricle, unable to take care of this inflow, becomes dilated and the syndrome of right ventricular failure develops. According to these investigators, dilatation of the right side of the heart, in the presence of clear lungs as evidenced by physical and roentgen-ray examinations, and the exaggeration of peripheral vascular signs after the administration of epinephrine and their diminution after pitressin constitute the main characteristics of "beriberi heart." The reports of Keefer [21] and others indicate, however, that the most common disturbances in "beriberi heart" in China are tachycardia, palpitation and excessive fatigue, and that pure right-sided dilatation is not an essential manifestation.

Aalsmeer and Wenckebach [10, 11] observed no essential electrocardiographic changes in patients with "beriberi heart" in Java. At times pa-

tients with severe circulatory disturbances showed a *shortened* P–Q conduction time, which became normal as the condition improved. Keefer [21] has described low voltage and negative T_3 waves in some of the cases observed in China.

Cardiovascular Changes in Experimental Vitamin B_1 Deficiency. So far as is known at present, deficiency of vitamin B_1 is the only vitamin deficiency which is followed by cardiac disturbances.* Carter and Drury [22] showed that pigeons fed a diet of polished rice developed bradycardia and heart-block. These changes were of vagal origin, as section of the nerve or atropine abolished them. In an electrocardiographic study of vitamin B deficiency in the rat, Drury, Harris and Maudsley [23] observed a bradycardia of 300 or 350 per minute, as compared with a normal rate of 500 to 525. In this animal the bradycardia was of sinus origin, and not due to vagal influence. So characteristic is this response that it is used to test diets for vitamin B_1 deficiency. These observations show that the cardiac disturbance can vary in different species.

The experimental studies did not reveal changes in the complexes of the electrocardiograms. As far as one can ascertain, however, the electrocardiograms obtained in rats were not standardized. Because the patients with nutritional deficiencies showed changes in the electrocardiographic complexes, a study was undertaken to ascertain whether similar changes develop in the standardized electrocardiograms of rats deficient in vitamin B_1.[24, 25] The results of this study indicate that rats on B_1 deficient diets develop not only bradycardia but also changes in the electrocardiographic complexes, such as increased height of the S–T segment and flattening or inversion of T–waves. Subcutaneous administration of from 5 to 28γ of crystalline vitamin B_1 (Merck) abolished within 6 to 12 hours both the bradycardia and the changes in the complexes. These electrocardiographic changes are in harmony with those described in human beings.

Central Nervous System Changes in Experimental Vitamin B_1 Deficiency. That deficiency of vitamin B_1 is associated with failure in certain oxydase systems has been known since 1918.[26] Peters and his associates [27, 28] have shown that in vitamin B_1 deficiency the oxygen utilization of the brain is reduced. After adding vitamin B_1 to deficient brain tissue of the pigeon and the rat in vitro, the oxygen consumption increased and the pyruvate formed by the avitaminous brain decreased. The degree of biochemical change was not the same in all parts of the brain. These workers concluded that the symptoms of avitaminosis observed in the rat and pigeon are of central origin.[28, 29] Church [30] has shown that the vestibular function is significantly altered in rats with vitamin B (B_1) deficiency. The fact that these striking changes in function, referable to vestibular nuclei, disappeared within as short a period as a few hours indicates that a central metabolic disturbance, rather than organic degenerative lesions, was responsible.

* It is probable that the myocardial disturbances reported in rickets and scurvy are caused by the simultaneous presence of vitamin B_1 deficiency.

Evidence of the Nutritional Origin of the Cardiovascular Dysfunctions. The following evidence supports the nutritional and particularly the vitamin B_1 origin of the disturbances of the cardiovascular system described: (*a*) In the majority of the cases studied there was unbalanced food intake with adequate supply of calories and with maintenance of normal body weight. A calculation of the vitamin B_1 content of the food in relation to the caloric intake was below the normal requirement of man and within the limit necessary for the development of B_1 deficiency, as indicated by Cowgill. The diet of these patients was therefore similar to that described recently by Jolliffe, Colbert and Joffe[18] in alcoholic addicts with polyneuritis. In a smaller group of patients the vitamin "B" intake seemed to be adequate but the presence of changes in the gastrointestinal canal apparently prevented its utilization. (*b*) None of the recognized etiological factors of cardiovascular disease were present in the "pure" cases studied. The clinical, physiological and morphological findings did not correspond to those observed in the recognized diseases of the cardiovascular system. (*c*) The cardiovascular disturbances were frequently associated with disturbances in other systems, which were of the type attributed to vitamin "B" deficiencies. (*d*) Just as in oriental beriberi, the patients with a severe degree of circulatory failure were not apt to have severe polyneuritis, and vice versa. (*e*) The dilatation of the peripheral arterioles, the relatively or absolutely increased velocity of blood flow with increased venous pressure, the dilated heart, the severe generalized edema, the vascular sounds associated with bounding pulsation, as well as the occurrence of vasomotor collapse, indicate a similarity between "beriberi heart" as described in the Orient and the condition observed in Boston. (*f*) The electrocardiographic changes observed in human beings are similar to those found in rats deficient in vitamin B_1. (*g*) All the characteristics of the disturbances observed in man usually disappear after rest and the administration of vitamin B_1 or a diet rich in vitamin B_1.

Differences Between the Circulatory Disturbances Observed and Those Reported in "Beriberi Heart." There were a number of differences between the characteristics of the cardiovascular dysfunctions observed in Boston and those described as "beriberi heart" in the Orient. In contrast to the patients observed by Aalsmeer and Wenckebach in Java, the group here reported usually did not exhibit a pure right-sided failure of the circulation. Patients with cardiac dilatation, peripheral arterial sounds, rapid peripheral flow and engorged veins were observed, but other patients with an identical type of deficiency showed pulmonary engorgement with dyspnea, cardiac asthma, orthopnea and other manifestations of left-sided failure. In a few patients vasomotor collapse developed in its pure form. Electrocardiographic changes with tachycardia were present in some patients without any other abnormality. There were again instances in which at different stages of the disease various combinations of these changes occurred.

Hence the cardiovascular disturbances caused by nutritional defects do not form a rigid clinical syndrome. We wish also to emphasize that the term "beriberi *heart*" is inappropriate because of the widespread nature of the circulatory disturbances in this disease. Wenckebach himself indicates that the primary change is a peripheral dilatation, and that the heart is only secondarily involved. Whether the clinical differences between oriental "beriberi heart," particularly as described in Java, and the cardiovascular disturbances in the group here reported are due to actual differences in some aspects of their pathogenesis, or to the fact that the type reported by Aalsmeer and Wenckebach represents but one form of the disease existing in Java, it is impossible to state. In the production of vitamin deficiencies in animals, factors other than vitamins play important rôles. In man, in the majority of instances there are multiple avitaminoses, and the number of variables is even greater. The composition of the food, the functions of internal secretory glands, the intensity of muscular work, and the time element in the development of the deficiency may well have an important bearing on the variability of the clinical picture. The relative significance of the interrelation between these factors is not known at present.

In the Orient it is recognized that persons who perform strenuous muscular exercise, and who do not exhibit polyneuritis, form the group which is liable to develop cardiac dilatation and other circulatory symptoms. In this part of the United States vitamin "B" deficiencies occur mainly in alcoholics, and less frequently in pregnant women, in persons without work and hence in poverty, in "food cranks," in patients with diabetes or with certain types of gastrointestinal diseases. Such persons seldom, if ever, perform prolonged hard work. This may well be important in determining the somewhat different aspect of the disease as observed in the Orient and in Boston. That deficiency of vitamins is not the sole determining factor in these clinical syndromes is clearly indicated by the fact that not all patients with the same degree of vitamin deficiency develop symptoms, and also by the fact that the same degree of deficiency can produce different symptoms in different subjects. Furthermore, pure vitamin deficiency, particularly a deficiency of B_1 (polyneuritis) or of B_2 (pellagra), is rare. In the majority of cases on record in the Boston City Hospital pellagra and polyneuritis occurred in combination. On the other hand, polyneuritis and pellagra were rarely associated with an *advanced* degree of scurvy.

Changes in the Electrocardiogram and Their Relation to Vitamin B_1. The electrocardiographic changes observed by us were essentially the same as those reported recently by Feil [31] in a group of patients with pellagra. It is significant, however, that in our group with nutritional deficiencies, electrocardiographic changes of identical nature were observed not only in pellagra without polyneuritis, but also in polyneuritis without pellagra, and in cases with food deficiency without either pellagra or polyneuritis. Contrariwise, electrocardiographic changes were not necessarily present in all pa-

tients with any of these deficiencies. In view of the fact that similar electrocardiographic changes were induced in rats with vitamin B_1 deficiency, and in patients without pellagra, we attribute the electrocardiographic changes to deficiency of vitamin B_1 rather than of other fractions of the "B" group. It is of interest and in harmony with observations in man that in the same rat the electrocardiographic changes may be different or may even be absent in repeated instances of vitamin B_1 deficiency. This is further evidence that in B_1 avitaminosis the disturbances even within one organ, such as the brain or heart, may vary, depending upon their particular focal localization.

Porter and Higginbotham [32] have claimed recently that not a single case of pellagra observed by them exhibited congestive failure of the circulation or increase in the size of the heart. They conclude that in pellagra no characteristic change occurs in the cardiovascular system and that pellagra and beriberi have no comparable effect on the heart. This difference, according to Porter's belief, is absolute and means that vitamin B_1 is not concerned with the pathogenesis of pellagra. He ventures that "many of the diseases produced by avitaminosis affect, in a selective manner, certain tissues of the body, and one can anticipate precisely the kind of deficiency by noting the structures involved and the character of the tissue reactions." Porter interprets the electrocardiographic changes observed in pellagra as having no relation to beriberi or to deficiency of vitamin B_1. In support of this he quotes Wenckebach's "unequivocal statement" that the electrocardiogram in beriberi is normal, with the exception that the conduction time is shortened. Such a contention is not in agreement with our findings. Our interpretation of our own observations, as well as of those of Feil and of Porter, is that the cardiovascular disturbances in vitamin "B" deficiencies are more varied than is claimed by Wenckebach in beriberi or by Porter in pellagra, and that deficiency of B_1 is the primary cause for all these disturbances. Cardiovascular disturbances are apt to be present in pellagra as well as in beriberi, because in man vitamin B_1 deficiency usually occurs in combination with B_2 deficiency.

The Rôle of Alcohol. As the majority of the patients observed consumed large amounts of alcohol, the rôle of alcohol in the development of cardiovascular manifestations requires special consideration. There is valid evidence indicating that alcohol per se cannot be primarily responsible for the manifestations observed. In the first place, chronic alcoholism is exceedingly common, while the condition described is relatively rare; hence a simple causative relationship does not exist. Furthermore, pharmacological studies do not reveal that pure alcohol per se causes persistent cardiovascular damage or polyneuritis, such as occurs in beriberi. In a group of patients with polyneuritis associated with alcoholism Strauss [33] has shown that the polyneuritis improved following the administration of vitamin B extracts and of amounts of alcohol similar to those consumed by

the patient during the development of the polyneuritis. Four patients of the group studied by Strauss, who are included in our series, showed cardiovascular changes which improved under the experimental therapeutic regime *containing alcohol.* Further evidence against the primary rôle of alcohol is that in spite of the fact that many of the patients with severe degrees of circulatory failure and polyneuritis discontinued the consumption of alcohol many weeks before the observations were made, the condition grew rapidly worse or actually developed during the withdrawal period. This was particularly true in patients with persistent anorexia, nausea, vomiting and diarrhea. If alcohol, a rapidly oxidizable substance, were a primary "toxic agent" this would not be likely to occur.

In the light of present knowledge, nevertheless, we attribute to alcohol the following *secondary* predisposing rôles in the precipitation of the cardiovascular dysfunctions and of vitamin deficiencies in general: (*a*) Alcohol is a food substance *par excellence* in this part of the world, and it supplies the body with the necessary calories but with a minimum of vitamin "B," an ideal combination of factors for the development of "beriberi." It should be recalled that the caloric value of a pint of pure alcohol is about 3,500 calories. In addition, the consumption of large amounts of alcohol tends to produce gastritis, achlorhydria, persistent nausea and diarrhea, which in turn further interfere with the utilization of vitamin "B." Such patients frequently claim that even with special effort they are unable to take appreciable amounts of food (Case 6). (*b*) There is possibly another specific, though secondary, rôle of alcohol in beriberi. It is known that the composition of the diet in terms of carbohydrate, protein and fat has a significant relation to the development of beriberi. Abderhalden and Wertheimer [34] have demonstrated that if vitamin B deficient pigeons are fed fatty acids instead of carbohydrates, muscular cramps characteristic of the deficiency do not develop. Several observers have claimed that a high carbohydrate diet in animals and a pure rice diet in man predispose to clinical vitamin B_1 deficiencies. Alcohol, as a carbohydrate, in large amounts may act in the same way. The tendency of diabetic patients to develop polyneuritis and cardiovascular dysfunction is probably due to the combined effects of an abnormal metabolism and a high carbohydrate, low vitamin diet.

The importance of alcohol in vitamin B deficiency has been demonstrated experimentally by the recent study of Wechsler, Jervis and Potts.[35] These investigators showed that the severity of the nervous symptoms of monkeys maintained on alcohol and a vitamin B_1 deficient diet cannot be referred to the avitaminosis alone. The clinical course of the B_1 avitaminosis was aggravated by continuous alcohol intoxication. They concluded that the combination of alcohol and B_1 avitaminosis is particularly noxious to the nervous system.

Pathogenesis of the Cardiovascular Dysfunctions. The results of

animal experimentation favor the concept that most of the manifestations of B_1 deficiency depend on disturbances of nervous functions, particularly in the central nervous system.[29, 30] The most frequent manifestations of beriberi in the Orient, as well as in the United States, consist in polyneuritis, psychosis, vertigo, cough and dysphagia, which are also nervous in origin. The question then arises as to whether the cardiovascular dysfunctions depend primarily on nervous, on local myocardial or on vascular changes. The instances of tachycardia followed by bradycardia, as well as the instances of irritable carotid sinus reflex, indicate that some of the manifestations depend on disturbance of the vagus system. The tendency to vasomotor collapse and the dilatation of peripheral arterioles, which constrict after the administration of crystalline B_1, may be, at least theoretically, central in origin. Some of the changes, especially those in the electrocardiogram, may be due to local myocardial disturbances. Other manifestations, such as cardiac dilatation, are explicable as secondary to the rapid peripheral blood flow. The exact pathogenesis of the cardiovascular dysfunctions, however, is not known at present.

The response of patients with beriberi to therapeutic measures also requires further study. Patients observed by us as well as those observed in China and in Labrador show considerable variation in rate of improvement. Moreover, in the same patient the dilatation of the arterioles and the prolongation of the electrical systole disappear promptly, the edema, decreased vital capacity and elevated venous pressures disappear more slowly, while the dilated heart and abnormal electrocardiographic complexes return to normal only after several weeks of treatment. These variations in rate of improvement indicate that in man primary vitamin B_1 deficiency, when chronic, is followed by secondary changes of slow reversibility. The gross and microscopic studies of the heart corroborate this contention. Cardiac dilatation and, occasionally, hypertrophy, "hydropic" degeneration of the myocardial fibers and increase in intercellular substance (collagen) are evidences of myocardial damage. That these do not represent simply "myocardial edema" is shown by the unaltered water content of the myocardium. Such a transition from chemical disturbances to physiological and ultimately to structural changes is not peculiar to the cardiovascular system in vitamin B_1 deficiency. Changes of a similar nature occur in the central and peripheral nervous systems and probably also in other organs. They are comparable to the disturbed functions and lesions of the nervous system, intestinal tract and skin in pellagra, and of the spinal cord in pernicious anemia.

Clinical and Therapeutic Implications in the Cardiovascular Dysfunctions Associated with Vitamin Deficiencies. The therapeutic indications for patients with definite vitamin deficiency are obvious. They should receive a well-balanced diet of adequate caloric value, rich in vitamin "B." In resistant or severe cases the parenteral administration of pure vitamin

B_1 or its extracts is indicated because such patients often suffer from anorexia with constipation or with diarrhea, and consequently have not only a low intake but also an impaired utilization of food.

It is well to bear in mind that patients with chronic organic heart disease may have, in addition, cardiovascular disturbances related to avitaminosis. The nutrition of patients with chronic heart disease, especially with congestive failure, is frequently poor. It is particularly important to give such patients a balanced diet rich in vitamins.

The doses of crystalline B_1 administered were larger than those indicated by experimental evidence. Such large doses were given mainly because there is available no clinical test which could be used as a guide for the adequacy of the dosage. It is of interest that no toxic reactions were observed, either in deficient or in non-deficient patients, following the intravenous administration of a dose as large as 50 mg. In some patients with dilated peripheral arterioles a temporary elevation of the arterial pressure followed the administration of crystalline vitamin B_1. Beneficial effects from crystalline vitamin B_1 were not observed in other diseases, including heart failure and edema, in which there was no vitamin B_1 deficiency.

Cowgill [9] has demonstrated that the tendency to develop polyneuritis varies directly with the metabolic rate of the body, and inversely with the vitamin B (B_1) intake; hence the conditions favorable for the development of " B " avitaminosis are quite different from those associated with general starvation and inanition. Because the available evidence also strongly suggests that the cardiovascular dysfunction is closely related to, if not caused by, vitamin B (B_1) deficiencies, any condition associated with prolonged high metabolism and low intake of vitamin B_1 will be particularly liable to result in clinical avitaminosis with cardiovascular disturbances. Strenuous work, hyperthyroidism and infectious diseases with fever are such bodily states. Hyperthyroidism is usually associated with an increased appetite and with the consumption of a well-balanced diet. In rare instances, however, it may be accompanied by anorexia and persistent diarrhea, and in such cases cardiac dilatation, polyneuritis and psychosis may be present. It is interesting that Chvostek [36] quotes the literature up to 1917 on the association of polyneuritis with hyperthyroidism. Means [37] also describes suggestive cases of hyperthyroidism and vitamin " B " deficiency.

It is known, and our experience bears this out, that to patients with deficiency polyneuritis and pellagra, both of the alcoholic and of the non-alcoholic type, infections in general, and pneumonia in particular, represent grave danger. The circulation in patients with infections is comparable to that in persons performing heavy and continuous exercise. Fever per se increases the work of the heart and the rate of the circulation. It also is associated with a rise in the metabolic rate and usually with anorexia, which further accentuate a preëxisting avitaminosis, as well as the associated cardiovascular dysfunctions. In a similar way the ordeal of general anes-

thesia and surgical operation may increase to the breaking point the strain on the heart and circulation of "B" avitaminotic patients.

The relation of vitamin B (B_1) to infection and high metabolism explains the origin of the infectious theory of beriberi, and the occurrence of "epidemics" of beriberi. Prolonged infections, such as malaria in the tropics, will tend to aggravate the existing deficiencies, and will bring to the surface underlying or "subclinical" deficiencies. In these cases therapeutic procedures which terminate the infection or reduce the fever, together with the administration of a well-balanced diet and vitamin B concentrate or parenteral preparations, may well be life saving.

The data here presented, we appreciate, do not offer final proof of a direct relationship between cardiovascular manifestations and deficiency of vitamin B (B_1) or of any other vitamin. This problem is still open, even as far as classical "beriberi heart" of the Orient is concerned. In this study an attempt was made only to present clinical evidence on the thesis that (*1*) cardiovascular disturbances do occur in association with vitamin "B" types of deficiency, often with adequate or more than adequate caloric intake; (*2*) while the clinical picture of this condition is variable, nevertheless it is similar in several respects to that of "beriberi heart" observed in the Orient.

The observations here described also serve to demonstrate that not only pellagra, but also beriberi, occurs in Boston. This completes the picture, showing that all known types of avitaminosis attributed to the vitamin "B" group, as well as to other types of vitamins, are present in the northeastern and probably other parts of the United States.

Summary and Conclusions

1. Dysfunction of the cardiovascular system resulting from unbalanced food intake is a disease of regular occurrence in the United States. This report is based on a study of 120 such cases, 35 of which were investigated within two years.

2. The cardiovascular manifestations depend on changes in the nervous system, in the vascular system and in the myocardium.

3. Tachycardia followed by bradycardia, gallop rhythm, vagal reflex irritability, dilatation of the heart, dyspnea, orthopnea and pulmonary congestion, associated with bounding arterial pulsation, arterial "pistol" sounds, engorged veins, warm skin and edema are the usual clinical features of severe cases.

4. The hemodynamics are characterized by low vital capacity of the lungs, high venous pressure and normal arterial pressure, and by a relatively or absolutely increased velocity of blood flow and decreased peripheral utilization of arterial oxygen. The osmotic pressure of the blood is usually moderately low and frequently remains essentially unchanged while the edema disappears.

5. The electrocardiograms were normal in but 7 per cent of 67 cases. The main abnormalities consisted in changes in the T–waves and prolongation of the electrical systole (Q–T). The electrocardiographic changes in patients with pellagra or beriberi probably are due to the B_1 component of the vitamin deficiency.

6. The myocardium often showed "hydropic" degeneration of the muscle and conductive fibers and increase in the intercellular substances, but unaltered water content.

7. The cardiovascular disturbances caused by nutritional deficiencies do not form a rigid clinical syndrome. Right ventricular failure, left ventricular failure, arteriolar dilatation and increased blood flow, peripheral circulatory collapse and shock, singly or in combination, have been observed.

8. The onset of the disease may be sudden or gradual. Patients with the severe form of the disease show a tendency to fever, to bronchopneumonia and to acute fatal circulatory collapse. Under therapeutic measures such as rest, cardiac drugs, diets rich in vitamin B_1 or crystalline vitamin B_1, all the cardiovascular disturbances usually revert to normal.

9. The clinical symptoms and signs, the blood chemistry, the myocardial changes, the hemodynamics and therapeutic responses correspond to those described in "beriberi heart" in the Orient. The disease as observed in Boston, however, is characterized by more varied and more generalized involvement of the cardiovascular system.

10. Evidence is presented indicating that vitamin B_1 deficiency plays a primary rôle in the precipitation of the disease. Alcohol also is a significant factor, not only because it supplies calories without vitamin B_1, but also because its metabolic effect is similar to that of a pure carbohydrate.

11. The rate of response to vitamin B_1 in "alcoholic" and "nonalcoholic" beriberi varies. The arteriolar system shows a more rapid change than the heart. The cardiovascular disorder usually disappears before the polyneuritis. The factors influencing therapeutic responses are discussed.

12. In normal subjects, as well as in patients with diseases other than vitamin B_1 deficiency, even large doses of crystalline vitamin B_1 produce no appreciable effects.

13. The condition here described bears pertinently on the clinical behavior and the mortality rates of alcoholic and nonalcoholic patients with vitamin "B" deficiencies (beriberi and pellagra). It may explain the poor reaction of these patients to increases in metabolic rate, such as occur in febrile infections, in hyperthyroidism, or under surgical operations. The therapeutic indications under these conditions are discussed.

This study was conducted with the assistance of Dr. Florence W. Haynes and Miss Sophia M. Simmons.

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AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR OF DOCTOR JOSEPH HERSEY PRATT

CHRONIC BILATERAL PYELONEPHRITIS: ITS ORIGIN AND ITS ASSOCIATION WITH HYPERTENSION *

By WARFIELD T. LONGCOPE, F.A.C.P., *Baltimore, Maryland*

THE continuous study of 22 cases of chronic bilateral pyelonephritis has led to the recognition of a number of complications and accessory factors that have been found to modify the usual course of this rather common disease. In a previous publication the significant symptoms and signs of the affection were described in some detail.[1] The essential characteristics of this form of pyelonephritis consist in its bilateral occurrence, usually without demonstrable or evident obstruction to the outflow of urine.[2] It is seen most frequently in young women between the ages of 15 and 30, but may occur in children or in older women. The youngest patient in this series among adults was 15 years of age, the oldest 55. The disease is usually of long duration. Symptoms of renal insufficiency may not appear for 10 or 15 years after the infection is first initiated. In seven of our patients the disease was known to have existed for at least five years or longer, and in three of them it had been present for from 14 to 17 years. During this long period leading up to the terminal stage, which manifests itself as protracted renal failure, the symptoms are usually slight and vague. Starting with a pyelitis in childhood, an infection of the urinary tract during pregnancy or, in rare instances, an outspoken acute pyonephritis there may be from time to time attacks of unexplained fever, with or without slight or fairly severe pain in the lumbar regions. These attacks are often accompanied by the passage of cloudy urine. Occasionally there is a history of albuminuria of many years' duration. Often there is a story of malnutrition, or sometimes of retarded growth in children, leading occasionally to rickety deformities. In some instances the progress of the disease is, for years, symptomless.

Unless the patient has symptoms or signs of renal failure, the condition is usually considered to be a chronic pyelitis. It is not until headache, nausea, vomiting, loss of weight, lassitude, dyspnea, or, in a few instances, convulsions, occur that the patient, in more or less desperate condition, is seen by a physician. Thirteen of our cases were not seen until the terminal stage of the disease was far advanced. Fourteen of these patients are known to have died, and in six of them the true nature of the disease was not recognized until autopsy which was obtained in 10 of the 12 cases.

It is possible, however, to determine the presence of the disease years before it is so far advanced. The signs that are of particular importance

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are as follows: There is often slight pallor, a rather dry skin, and frequently a tendency to underweight. Edema is extremely rare, except when myocardial failure complicates the later stages of the disease. Unless hypertension supervenes, the heart is not enlarged. The blood pressure is not often elevated during the early stages of the disease. The systolic blood pressure was below 125 mm. and the diastolic below 85 mm. of Hg in five of nine cases which were seen at this period.

As the disease advances it is usual to find that the blood pressure rises. This is not, however, an invariable occurrence, for in at least three fatal cases the blood pressure remained essentially normal. In one woman of 21 the highest recorded blood pressure was 118 systolic and 68 diastolic; in a man of 24 the blood pressure varied between 120 systolic with 78 diastolic and 145 systolic with 75 diastolic; and in a boy of 15, the highest pressure was 140 systolic and 90 diastolic.

These instances should be recorded as exceptions rather than as exemplifying the rule, for usually the blood pressure rises during the latter months or years of the disease and may reach such high figures as 225 mm. of Hg systolic and 150 mm. Hg diastolic.

The retina usually show no changes until the disease is far advanced or has actually reached the terminal stage.

At times there is costo-vertebral tenderness. The urine is passed in fair quantities, the specific gravity is constantly low and with the progress of the disease becomes practically fixed at a figure near 1.010 or 1.012. The urine contains traces or moderate amounts of albumin, rarely casts or red blood cells, but many leukocytes which vary in numbers from time to time. In the great majority of patients cultures from the urine give at some time a growth of *B. coli*. In a few patients this organism was constantly present, but more often it appeared only at intervals. Though the early stages of the process may not be accompanied by any definite impairment of renal function, a striking feature is the unexpected frequency with which a marked impairment of renal function occurs at a time when the patient feels perfectly well. Months or even years before the terminal stage, the non-protein nitrogen of the blood may be distinctly elevated above normal, the phthalein output greatly reduced, and the curve of excretion flattened; the specific gravity of the urine fixed at a low level, and the urea clearance far below normal. In one patient who has been under observation for 7½ years, the non-protein nitrogen of the blood has never fallen below 42 mg. per 100 c.c. and has at times reached 50 mg. per 100 c.c., the specific gravity of the urine has been constantly fixed between 1.001 and 1.004, the phthalein output has gradually fallen from 60 per cent to 47 per cent, and the urea clearance from 42 per cent to 21 per cent of the normal standard. During all this time the patient, except for occasional headaches and attacks of lumbar pain, has felt well and been constantly at work. In another patient the non-protein nitrogen of the blood remained about 74 mg. per 100 c.c. for three years before

death, and in a third patient, who has recently died, the non-protein nitrogen of the blood has varied between 55 mg. per 100 c.c. and 88 mg. per 100 c.c. for three years. During this protracted period of renal insufficiency there are rarely any of the symptoms that can be ascribed to this defect.

In some of these patients who display such long periods of renal insufficiency, the urine remains neutral or slightly alkaline. This may occur in the absence of evidences of cystitis and when the urine is sterile. In such

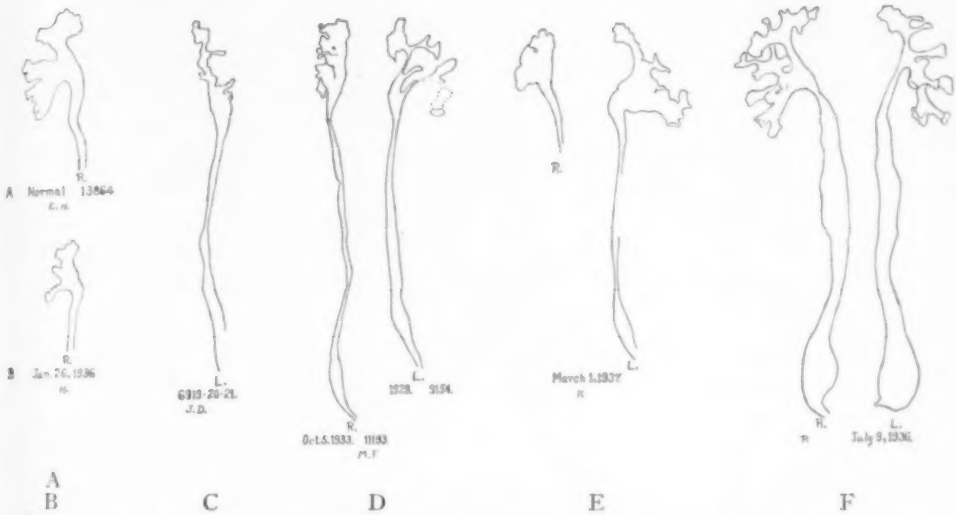

FIG. 1. Case 2. (No. 20 in table). Outlines of pyelograms of kidney pelves showing dilatation of ureters.

A. Outline of pyelogram from right normal kidney.
B. Outline of pyelogram from right kidney Case 12. Table I.
C. Outline of pyelogram from left kidney Case 5. Table I.
D. Outlines of pyelograms from Case 1. Table I.
E. Outlines of pyelograms from Case 1 text (Case 18. Table I).
F. Outlines of pyelograms from Case 2 text (Case 20. Table I).
Showing marked dilatation of ureters and pelves.

patients it may, in fact, be impossible to produce an acid urine, either by the administration of ammonium chloride or by a ketogenic diet. This occurred in one of our patients who developed symptoms of acidosis, with a reduction of the CO_2 combining power of the serum to 29.6 volumes per cent, and still excreted urine which was alkaline or neutral in reaction.

One of the most important evidences of the disease is obtained by pyelography. The characteristic change observed in the pyelogram is a distortion, flattening and reduction in the size of the pelves (figure 1). This may occur without dilatation of the ureters, though in some instances there may be uniform or irregular dilatation of the ureters. An actual enlargement of the pelves of the kidneys is rare. The cystoscopic examination shows, as a rule, no changes in the bladder, though in one case ulceration of the mucosa was observed.

A combination of these various features produces a clinical picture which has such distinctive characters that one is usually able to recognize the disease, even though it occurs in patients who are apparently in excellent health.

The pathological changes in the kidneys which have been so frequently described [3, 4, 5, 6] suggest that the progress of the disease is caused through the gradual destruction and elimination by inflammation and scarring of small portions of the kidneys. The intervening parenchyma remains comparatively normal in appearance and apparently functions adequately. The kidney fails completely when this process of amputation reaches a point that is incompatible with life, or when a complication such as arteriolar sclerosis, or acute diffuse glomerular nephritis, is superimposed upon the renal structure that is already seriously damaged. Death may also occur from some intercurrent infection, but in all of our fatal cases uremia closed the picture.

It is of great importance to determine the exact manner in which the disease arises. In the majority of cases cultures of the urine and from the pelves of the kidney show a growth of *Bacillus coli*, and it is to be presumed this organism causes the original and the persistent infection. A gross inflammation of the mucous membranes of the bladder, such as commonly occurs in strictures of the urethra or prostatic hypertrophy is not present. There is rarely any evidence of gross strictures of the ureters though in cases of long duration points of narrowing, particularly in the portion that courses through the wall of the urinary bladder, may be present. It is in these cases that irregular dilatation of the ureters may be found. It is extremely difficult to determine, once the disease is well established, whether these anatomical strictures originally predisposed to an ascending infection of the urinary tract, or simply occur as a complication of the long continued passage of infected urine from the kidney. There is, however, considerable evidence to indicate that in infants and young children, so-called pyelitis is actually an acute pyonephritis, arising bilaterally from hematogenous infection of the kidneys. (Bugbee,[7] Chown,[8] Wilson and Schloss,[9] Band, Dunlop, and Dick.[10])

It is very difficult to obtain definite information on this point in the adult, but the following cases seem to indicate that acute pyonephritis may occur in adults as a primary disease presumably from hematogenous infection of the kidneys by *Bacillus coli*, and further that recovery from the acute phase may be followed by intermittent pyuria due to *Bacillus coli*. The first case must exemplify a very unusual situation.

Case 1 (No. 18 in table). A young unmarried white girl, 16 years of age, was admitted to the Johns Hopkins Hospital on September 27, 1936, complaining of cramps in the stomach and dysentery. Her father had died of cancer of the rectum. For seven or eight years she has been subject to attacks of abdominal cramps which have come on every few months. They have lasted two to three days. Eight days before admission she had one of these attacks which was very severe. Three days after the onset of this attack her eyes had become swollen, and a day or two later her hands and feet were also swollen.

Physical examination showed a pale undernourished girl with temperature 100.6°, pulse 116, respirations 18. There was moderate anasarca, with swelling of face and pitting over shins. The fundi oculi showed increased shimmer of retina. Lungs were clear to percussion and auscultation. Heart was not enlarged and there were no murmurs. Blood pressure was 120 systolic and 85 diastolic. Abdomen was distended and tender. Liver, spleen, and kidneys were not palpable. Slight clubbing of the fingers was noted. Red blood cells 1,870,000; hemoglobin 39 per cent; white blood cells, 8,520; polymorphonuclear leukocytes, 60 per cent. Urine was acid, 1.010 specific gravity, there were large amounts of albumin—7 grams per liter, many granular and leukocytic casts, few red blood cells and great numbers of leukocytes. September 28, non-protein nitrogen of blood was 80 mg. per cent; total plasma proteins 4.81 gm. per cent; albumin globulin ratio 60/40. Blood culture made September 29 showed no growth. Culture of urine on September 30 showed growth of *Bacillus coli*. On this day a transfusion was given. October 2, phthalein excretion was 12 per cent in two hours; October 3, phthalein excretion was 24 per cent in two hours. Temperature remained elevated from September 27 to October 17. She continued to have severe abdominal cramps and diarrhea. On October 5, the non-protein nitrogen of blood was 76 mg. per cent, and urea clearance 25 per cent of normal standard.

After October 5, there was some improvement. The edema diminished and finally disappeared by October 11. The albumin decreased to a small amount by October 9, but casts, red blood cells, and leukocytes continued in large numbers in the urine. There was rapid improvement in renal efficiency. By October 12 the non-protein nitrogen of the blood had decreased to 34 mg. per cent, and on October 13, the phthalein was 72 per cent in two hours. By October 15 the non-protein nitrogen of the blood was 30 mg., and the urea clearance 64 per cent of maximum standard. Cultures from the urine continued to show heavy growth of *Bacillus coli*. At this time proctoscopic examination showed great numbers of polyps in the rectum and roentgen-ray of the colon demonstrated multiple polyposis, which was believed to explain the attacks of abdominal cramps and diarrhea that she had had for many years.

She was given ammonium chloride for a few days until the urine became sufficiently acid (pH 5.5), and, on October 18, 12 gm. ammonium mandelate were administered daily for five days. By October 22 cultures of the urine showed no growth of *Bacillus coli*. Subsequently cultures from October 27 to November 2 were sterile. The albumin, red blood cells, and leukocytes rapidly diminished in the urine. For a few days the casts increased. November 2 to 6 the urine contained either traces of albumin or no albumin, occasional leukocytes, no red blood cells, and occasional hyaline casts. On November 29 the phthalein was 93 per cent. November 10: Hemoglobin 80 per cent, red blood cells 4,070,000. Since this time, as the chart (chart 1) shows, there have been recurrences of the bacilluria, controlled temporarily by the use of ammonium mandelate. Pyelograms made in March 1937 showed no abnormalities (figure 1 E).

It seems evident that this girl was suffering from an acute pyonephritis due to *Bacillus coli*. The renal infection was possibly hematogenous and secondary to an inflammation of the colon associated with multiple polyposis. Rapid sterilization of the urine and complete recovery from the acute pyonephritis followed the administration of ammonium mandelate, but subsequent cultures from the urine have given at intervals a growth of *Bacillus coli* indicating that the infection of the kidneys has not been eradicated. This patient not only illustrates one mode of origin of chronic pyelonephritis, but exemplifies in a striking manner the immediate benefit derived from the

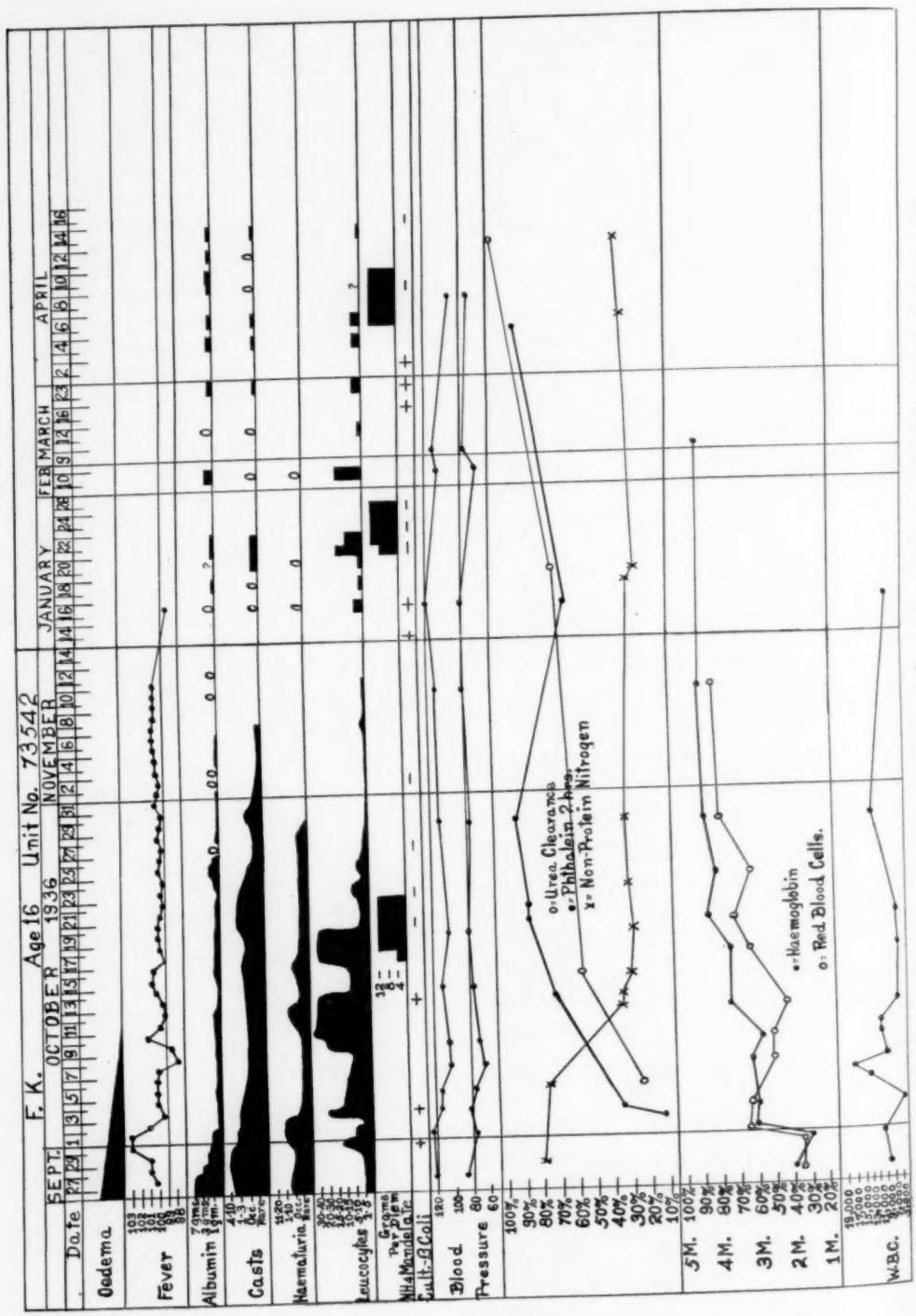

CHART 1. (Case 1 text) showing course of illness of F. K. from September 1936 to April 1937.

use of ammonium mandelate in infections of the urinary tract by *Bacillus coli.*

Though it seems probable that this mode of onset may account for the origin of the disease in many, if not the majority of cases of this type of bilateral pyelonephritis, it is quite possible that some form of obstruction to both ureters may predispose the kidneys to infection. The enlarged uterus of pregnancy might act in this manner. In rare instances, congenital stricture or unexplained bilateral dilatation of the ureters, such as has been described by Ellis and Evans,[11] might produce the same result. The following case may be an example of this latter condition.

Case 2 (No. 20 in Table). A white married man, 29 years of age, was admitted to the Urological Service of the Johns Hopkins Hospital on June 24, 1936. (For the early records I am indebted to Dr. H. H. Young.) He complained of "kidney pain." He came of a healthy family and had usually been well. He could not recall any past illnesses except measles and mumps as a child. There had been no urinary disturbances. Married eight years, his wife had had no miscarriages; he denied any venereal infection. While in perfect health he suddenly developed pain in the epigastrium and both kidney regions nine weeks before admission (May 1936). The attacks were repeated but did not prevent his working. He soon developed jaundice, lost appetite, was nauseated and vomited. Jaundice lasted about two weeks and as it disappeared he improved, but attacks of pain persisted. Two weeks before admission (about June 10, 1936) pains became particularly severe, his temperature rose to 103° and he went to bed. Nocturia appeared without dysuria; he had chills and fever, and the pain became worse.

On admission his temperature was 102° F., blood pressure 195 systolic and 112 diastolic, pulse 72. He was somewhat undernourished. There was no edema. Lungs were clear to percussion and auscultation; the heart was not enlarged; the PMI was 7.5 cm. to left of midline in the fourth interspace. There were no murmurs. There was tenderness in the costo-vertebral angles, over the kidneys, and to the left and below the umbilicus. Liver edge was readily palpable, spleen not felt. The prostate was small and not tender. Hemoglobin was 94 per cent, leukocytes 12,500. The urine was acid, amber, sp. gr. 1.020; no sugar; albumin 2+; no casts; rare red blood cells. Wassermann reaction was positive. On June 25, phthalein excretion was 89 per cent, non-protein nitrogen of the blood 60 mg. per 100 c.c. Culture of the blood showed less than one colony per c.c. of *Bacillus coli;* culture of the urine showed *Bacillus coli.*

An irregular temperature persisted with continuation of the pain. By June 26 blood pressure had fallen to 128 systolic and 70 diastolic; blood urea 32 mg. per 100 c.c. The urine continued to show small amounts of albumin and pus, but only occasional casts. Blood cultures made on July 1, 3, and 5 showed no growth. Cystoscopic examination showed no abnormality of the bladder; the ureters could be readily catheterized; cultures of urine from both ureters showed *Bacillus coli.* Phthalein appeared in the urine from both ureters in five minutes; 25 per cent was excreted from the left and 35 per cent from the right in 30 minutes. Ureteral catheters were left in place. There was excellent drainage from both sides, but the patient continued to have chills and fever. Retrograde pyelograms on July 9 showed marked dilatation of the lower portions of both ureters with pelves that appeared normal (figure 1 F). There were no calculi.

He was admitted to the Medical Wards on July 12, 1936. At this time the blood pressure was 120 systolic and 72 diastolic; he showed loss of weight and some anemia.

CHART 1. (Case 1 text) showing course of illness of F. K. from September 1936 to April 1937.

The hemoglobin was 76 per cent; red blood cells 3,600,000; but there was no increase in leukocytes, 8,000. There was still fever, and there was tenderness to deep pressure in both flanks. The urine was alkaline, sp. gr. 1.001; with traces of albumin and much pus, but no casts. There was fever with daily rises of temperature from 99.4° to 102.4°.

On July 13 the non-protein nitrogen was 25 mg. per 100 c.c.; the CO_2 combining power of the serum 65.3 per cent; and a culture from the urine showed heavy growth of *Bacillus coli*. A culture from the blood gave no growth. The patient was placed on 3 grams of potassium iodide a day, and seven days later the temperature was lower, the fever disappearing after the twelfth day. He was discharged on July 29, 1936, but returned to the hospital on November 13, 1936, saying that he had received eight injections of arsphenamine and eight injections of bismuth in the interval. He had felt well, working daily until three days before admission (November 10), when he experienced dull pain in the lumbar region and in the epigastrium, and felt chilly. The pain grew worse and he had chills, fever, sweats, and frequency of urination. On admission the temperature was 104°, pulse 92. The skin was dry, the lungs clear, the heart not abnormal, and the blood pressure 120 systolic and 60 diastolic. There was tenderness in the costo-vertebral angles and in both lumbar regions; the liver was palpable, the spleen not felt. There was no edema. The hemoglobin was 100 per cent; red blood cells 4,700,000; leukocytes 12,750. Urine was cloudy, pale, sp. gr. 1.007; acid; showed no albumin; no casts, but great numbers of leukocytes; cultures gave a heavy growth of *Bacillus coli*. November 14, non-protein nitrogen of the blood was 30 mg. per 100 c.c. November 15, phthalein excretion was 70 per cent in two hours. November 18, urea clearance was 68 per cent of normal standard. By November 17 temperature had fallen precipitately to normal, and traces of albumin and much pus appeared in the urine. In an effort to combat the urinary infection after a preliminary course of ammonium chloride (6 to 8 grams a day) from November 15 to November 21, when the required urinary acidity of at least pH 5.5 was obtained, ammonium mandelate was administered in doses of 12 grams a day from November 21 for 14 days without definite effect, for *Bacillus coli* was cultivated persistently from the urine from November 14 to December 9, five days after the course of ammonium mandelate. There was, however, gradual symptomatic improvement. On December 1, 1936, the non-protein nitrogen of the blood was 32 mg. per 100 c.c., the blood pressure 130 systolic and 80 diastolic, and on December 6 the phthalein excretion was 50 per cent in two hours. On December 10 cystoscopy showed a granular cystitis, the ureters could be readily catheterized, the ureteral orifices were dilated by bougie. Pyelograms made again on December 10 were similar to those obtained on July 9 and showed no abnormality of the pelves, but a dilatation of the ureters affecting particularly the lower portions (figure 1 F). On January 2, non-protein nitrogen of the blood was 32 mg. per 100 c.c. January 4, cultures from urine again showed *Bacillus coli*. Following a preliminary period of ammonium chloride a second course of ammonium mandelate was started on January 5, but this could not be completed for the patient left the hospital on January 9, 1937.

It seems more than probable that this case is illustrative of an acute pyonephritis arising from an hematogenous infection by *Bacillus coli* in a patient who was already the subject of an abnormality of the urinary tract consisting of bilateral dilatation of the ureters due perhaps to some congenital anomaly. It is impossible, however, to exclude the urinary tract as the primary seat of infection with an invasion of the blood subsequently by *Bacillus coli*.

The acute illness in this patient may be regarded as the onset of a serious

and perhaps progressive infection of the kidneys and renal pelves, for it has not, so far, been possible to eradicate the infecting organism.

It has been pointed out that as the bilateral chronic pyelonephritis progresses there is a distinct tendency for the blood pressure to rise. The blood pressure was above 160 systolic and 105 diastolic in 10 of 15 patients who were observed during the advancing or terminal stages of the disease. In half of these the systolic pressure was 200 or over, and in 10 the diastolic pressure was between 110 and 150 mm. of Hg. The gradual rise of blood pressure from comparatively normal levels (105/60 and 146/90), during the early stages, to high levels (200/118 and 162/102) in the later stages could actually be followed in two patients.

On the other hand, in seven cases, including the two patients referred to above who were observed during a comparatively early stage of the disease, only one showed a systolic blood pressure over 140 or a diastolic blood pressure over 85 (146/90). The highest systolic pressure in five of these patients was not above 120, or the diastolic pressure above 85, while in four the highest diastolic pressure was not above 80 mm. of Hg. In one patient the highest blood pressure was 138 systolic and 78 diastolic.

Since the hypertension comes as one of the late manifestations of the disease, it is important to learn whether it is due to a complicating arteriolar disease or whether it is to be considered as an essential part of the clinical picture and is related directly to the failing renal function itself.

It is hardly possible to accept the latter suggestion without some reservations, for it was found that the blood pressure was within normal limits or only slightly increased in seven patients in whom the evidences of renal failure were pronounced as measured by the retention of non-protein nitrogen, the excretion of phthalein, or the urea clearance. Five of these patients died. In four the systolic pressure never rose above 145, and in one varied between 110 and 170. One patient is living and the fate of the other is unknown. Four of the fatal cases came to autopsy.

On the other hand, if one inquires into the combination of hypertension with hemorrhagic retinitis and arteriolar lesions of the fundus, it is found that the relationship is quite striking. Table 1 gives the results of this study. Dr. Arnold Rich has very kindly examined the organs of the cases that have come to autopsy, with special reference to the condition of the arterioles. It has, therefore, been possible to add the valuable information obtained from him to the study of Cases 5, 6, 7, 8, 9, 11, 15, and 16 (table 1).

It may be seen that in 11 of the 12 patients who showed any elevation of blood pressure above normal, pathological lesions in the arteries and arterioles of the retina were observed during life in all but one. The arteriolar disease was combined with hemorrhages in eight cases and with hemorrhages and exudates in four patients. On the other hand, in seven cases seen during the early stages of the disease when the blood pressure was

TABLE I

No.	Sex	Age	Duration	Blood Pressure	N.P.N. mg. %	Urea Clearance % Normal	Retinal Lesions				Living	Dead	Autopsy			Remarks
							Arterio-sclerosis	Edema Discs	Hemor-rhages	Exudates			Pyelo-nephritis	Arteriolo-sclerosis	Glomer-ular Nephritis	
1.	F	34	7 yrs.	146/92	50	21	++	0	+	0	+					
2.	F	26	7 yrs.	105/60–200/118	128	6	++	0	0	++		+				No autopsy
3.	M	19	16 yrs.	120/70–140/70	140	9	0	±	0	0	?					
4.	F	21	7 mos.?	110/60–118/68	70	7	++	±	+++	0		+				No autopsy
5.	F	18	14 yrs.	175/135–225/150	130	3	+++	++	+++	+++		+	+++	±	0	
6.	M	24	9 mos.?	120/78–145/75	312	2	0	0	0	0		+	+++	0	0	
7.	F	28	3 weeks?	160/90–170/110	250		++	+	+	0		+	+++	+	0	
8.	F	15	3 yrs.+	110/60–120/80	168–244		0	0	0	0		+	+++	0	0	
9.	F	36	17 yrs.	160/100–230/140	40	40	++	±	0	0		+	+++	+	0	
10.	M	23	?	116/70–110/75	46	52	0	0	0	0	+					Early
11.	F	37	4 mos.+	200/110	170		±	0	0	0		+	+++	±	+++	
12.	F	22	?	140/80–180/120	116	5	±	+	++	++		+				No autopsy
13.	F	52	1 yr.+	138/90–170/110	220	4.5	±	0	0	0		+				No autopsy
14.	M	15	3 yrs.+	140/90	304		±	±	+	0		+	?	0	+++	
15.	F	26	7 yrs.	162/112–226/108	112	13.5	±	+	++	++		+	++	+	+++	
16.	F	55	3 mos.?	110/80–170/110	96		±	±	+	0		+	+++	0	0	
17.	F	58	?	165/80–206/110	55–88							+				Hyperparathyroidism; no autopsy
18.	F	16	5 days	120/80	80–32	25–70	0	0	0	0	+					Acute
19.	M	45		155/100	90–50		0	0	0	0						Hyperparathyroid
20.	M	29	8 mos.	120/60	30	68	0	0	0	0	+					Early
21.	F	44	4 yrs.?	94/60–110/85	34–53	49–42	0	0	0	0	+					
22.	M	23	?	135/78	60	35.5	0	0	0	0	+					

within normal limits, except in one patient when it was 140 systolic and 85 diastolic, the fundi were normal. In this one patient slight alterations were observed in the arterioles. In spite of the normal blood pressure and the normal appearance of the fundi oculi, the renal function was definitely impaired in four. In the seven patients seen during the latter stages of the disease, in whom the blood pressure was either within normal limits or only slightly elevated but in whom the renal function was markedly depressed, pathological changes were seen in the fundus in only three, in two of whom the pressure was slightly elevated.

It seems, therefore, that the ophthalmological picture of retinal arteriolar sclerosis and hemorrhagic retinitis is much more nearly related in these patients to the hypertension than to the presence or degree of renal insufficiency.

The results of the microscopical examinations of the organs at autopsy are as follows: All cases showed a marked and extensive pyelonephritis. In

no case, however, could Dr. Rich find, in addition to the pyelonephritis, pronounced or extensive hyaline sclerosis of the arterioles of the kidneys or other organs such as the pancreas, adrenals, and intestines.

In the four fatal cases (6, 8, 14, and 16) in which the blood pressure remained within normal limits or was only slightly elevated, sometimes only at intervals, the arterioles of the kidney, pancreas, adrenals and intestines appeared normal. In one case (14) there was a complicating and definite glomerular nephritis. In three cases in which hypertension was marked and was one of the outstanding features of the clinical course a few arterioles were found in the kidney, pancreas, adrenals and intestines which showed moderate hyaline sclerosis, but the lesions were almost minimal in extent. One of these patients showed extensive hemorrhagic retinitis with retinal exudates (Case 5, fundi). A second showed extensive hemorrhagic retinitis with pronounced lesions in the arterioles and the third presented well marked changes in the retinal arterioles, without hemorrhages, exudates or edema. Two patients (11 and 15), both with pronounced hypertension, showed in addition to the extensive pyelonephritis a diffuse and advanced glomerular nephritis with moderate to minimal hyaline sclerosis of the arterioles in the kidney, pancreas, and adrenals. One of these patients (11) was not observed to have retinitis though the retinal arteries showed abnormalities; the other (15) showed marked lesions of the retinal arterioles with fairly extensive terminal hemorrhagic and exudative retinitis.

One must conclude from a study of this short series of fatal cases that widespread and extensive arteriolar sclerosis did not occur. Scattered and sometimes minimal hyaline sclerosis of the arterioles of the kidney, pancreas and adrenal was found in five of the fatal cases who during life had markedly elevated blood pressures. In two of these cases there proved to be, in addition, a diffuse chronic glomerular nephritis. In the four cases in which hyaline sclerosis of the arterioles was not seen in sections of the organs, the blood pressure during life was within normal limits in one and only slightly elevated in the others. In one of these latter cases a diffuse chronic glomerular nephritis was found at autopsy (14).

It appears, therefore, that the hypertension which was found to exist in the terminal stages of the disease, or was observed to develop during the course of the disease in two patients, was not associated with pronounced arteriolosclerosis of the vessels of the kidneys, or with widespread uniform involvement of the arterioles of other organs. In spite of the marked hypertension and the lesions in the fundi, which were present during life in several of these patients, the pathological lesions at autopsy were not as extensive as those usually observed in arteriolosclerosis. Unfortunately the fundi were only examined histologically in one case. In this patient (Case 5) the blood pressure varied from 180 systolic and 150 diastolic to 225 systolic and 150 diastolic; there was cardiac hypertrophy with myocardial insufficiency as a terminal event. It was noted by the late Dr. William H. Wilmer that

the optic discs were swollen, the arteries narrow, tortuous and irregular, and that there were many hemorrhages and exudates in the choroid. The picture was considered by him to represent vascular sclerosis of the retinal and choroidal vessels. This histological examination of the retina was made of several sections cut at different levels through both orbits. They showed that there was edema of the nerve head, with several hyaline arterioles in the nerve head. There were no hyaline arterioles in the retina, no hemorrhages or exudates, but several small scars which may have been the result of organized hemorrhages or exudates. Such marked incompatibilities are certainly not usual, and it is difficult to understand why abnormalities during life, which are, as a rule, associated with arteriolosclerosis should prove, at autopsy, to be accompanied with so few anatomical lesions.

Unfortunately lumbar puncture was not performed in these patients, and no information is available, therefore, concerning the pressures in the spinal fluid. In view of Pickering's [12] observations upon the association of albuminuric retinitis with high spinal fluid pressures, it would have been valuable to have data upon this point.

It was often noted that the height of both the systolic and diastolic blood pressures changed considerably from time to time in many of these patients. In Case 9 there were variations from 160/100 to 230/140; in Case 12 from 140/80 to 180/120; in Case 13 from 138/90 to 170/110; and in Case 16 from 110/80 to 170/110. Although this is not uncommon in some instances of arteriolosclerosis it is observed more often in patients who are suffering from the form of hypertension generally designated as essential. It is also to be remarked that retinal hemorrhages were much more common (8 cases) than exudates (4 cases), and that swelling of the optic disc, though frequent (9 cases), was rarely marked.

One might therefore conceive of the condition as being somewhat different from the classical forms of arteriolar disease. Although it is impossible to correlate satisfactorily the elevation of blood pressure with the presence or intensity of renal insufficiency, it is to be noted that retinal hemorrhages and exudates were only found in those patients who showed evidences of marked renal impairment.

The experimental work of Goldblatt and his coworkers [13] has shown that ischemia of the renal tissues of dogs and monkeys [14] produced by reducing the arterial flow of blood to the kidney through constriction of the renal arteries, results in a persistent elevation of blood pressure. Even constriction of the arterial flow to one kidney may, and usually does, result in a definite increase in blood pressure, though the rise is much greater and of longer duration when both renal arteries are constricted.

This work has been amply confirmed by Page,[15] Elaut [16] and by Wood and Cash.[17] Page has shown that denervation of the pedicle of the kidneys does not prevent the rise of blood pressure following the Goldblatt operation, and Goldblatt [13] reports that excision of the dorsal sympathetic ganglia and splanchnic nerves does not reduce the blood pressure in his dogs.

The experiments of Tigerstedt and Bergman [18] upon the presence of a pressor substance in the kidneys of rabbits designated by them "Renin" have been repeated and modified by Harrison, Blalock, and Mason,[19] and by Prinzmetal and Friedman.[20] The former authors found that extracts of the kidneys of normal dogs usually produced moderate transient increases in blood pressure when injected intravenously into unanesthetized dogs, but that extracts of kidneys from dogs made hypertensive either by ligation of the ureters or by the Goldblatt method produced a much greater rise in pressure than the extracts from normal kidneys. Prinzmetal and Friedman not only compared the extracts from the two kidneys of dogs, after one renal artery had been constricted with resulting hypertension, but compared the effects of extracts from the kidneys of patients who had died with benign and malignant hypertension, chronic glomerular nephritis, and from chronic pyelonephritis with extracts of normal human kidneys. It was found that the extracts of the abnormal kidneys from both dogs and human beings were usually much more potent in their ability to raise the blood pressure when injected intravenously into dogs than the extracts of normal kidneys.

It is not understood how renal ischemia or the injection of extracts of diseased kidneys cause hypertension, but the results suggest that the pressor substance present normally in the extract from the cortex of the healthy kidney is much increased in the diseased kidney. Whether these experiments and observations have any bearing on the hypertension developing during the later stages of chronic pyelonephritis with contracted kidney it is not possible to say, but there are analogies which are highly suggestive in the two sets of conditions.

It is a matter of particular interest that constriction of only one renal artery in dogs will result in a moderate degree of hypertension which may persist for some time. Both Jacoby [5] and Haslinger [4] report instances of unilateral "Schrumpfniere" due to chronic pyelonephritis and the condition does not seem to be extremely rare. It may occur in individuals in whom a chronic infection of the kidney occurs in relation to a renal calculus imbedded in one of the calyces of the kidneys. One such case has come under my observation. In this patient the unilateral pyelonephritis was associated with hypertension. The blood pressure varied from 210/120 to 140/100. There was no evidence of renal insufficiency for the phthalein excretion was 90 per cent in two hours, the non-protein nitrogen of the blood 30 mg. per cent, the urea clearance 63 per cent of the normal standard, while the specific gravity of the urine varied from 1.006 to 1.030. The question naturally arises, however, as to whether disease, such as this, of one kidney could produce a persistent elevation of blood pressure in man.

Conclusions

The contracted kidney of chronic pyelonephritis may arise in adults, as it is said to arise in infants and children, from a hematogenous infection of

the kidneys. The bacterium which is usually responsible for this infection is *Bacillus coli.*

The onset of the disease may assume the form of acute pyonephritis.

The disease progresses insidiously for years but may be recognized in many patients during this insidious stage by special methods of examination.

During the latter phases, the chronic renal insufficiency is often, but not always, combined with intermittent or persistent hypertension.

Hemorrhagic retinitis occasionally with exudates may occur at this time.

The hypertension was not associated with pronounced or extensive arteriolosclerosis in nine fatal cases which came to autopsy, for among six of these patients who had an elevated blood pressure during life only five showed any arteriolosclerosis at autopsy, and in two of these it was minimal in degree and in extent. In three of the fatal cases the chronic pyelonephritis was combined with a chronic diffuse glomerular nephritis.

The explanation for the hypertension occurring particularly during the latter stages of the contracted kidney of pyelonephritis is not clear.

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AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR OF DOCTOR JOSEPH HERSEY PRATT

PRIMARY INFLAMMATION OF ARTERIES *

By HOWARD T. KARSNER, M.D., F.A.C.P., *Cleveland, Ohio*

ARTERIES may become inflamed because of the extension of neighboring inflammations or because of the action of bacteria or parasites brought to the site from some more or less remote portal of entry. The disease is due to the presence of the infective agents and their products. There are other forms of arteritis which appear to be independent of the immediate presence of infectious organisms. Ultimately both these forms of arteritis are probably due to the products of the organisms, but there is at least an academic difference between those in which bacteria are found in the inflamed focus and those in which they are not. Similar lesions are found without known infection in the body. Furthermore, there are some in which hyperergic phenomena seem to play an important part. It is proposed to apply the term secondary arteritis to those in which infective agents are present and the term primary arteritis to those in which these agents are not demonstrable.

Vascular changes in acute infectious diseases have been extensively studied and much of the pertinent literature is reviewed by Karsner and Bayless. Degenerative and mild or severe inflammatory lesions of the arteries, not directly caused by an infective agent, are well known, but few if any correlative studies have been published. The original account of periarteritis nodosa by Rokitansky in 1852, correlated with the clinical aspects by Kussmaul and Meier in 1866, has been followed by many publications on arterial inflammations, in which the term has been employed to designate several varieties of necrotizing † and exudative arteritis. Critical examination of several reports shows that what is called periarteritis nodosa by the authors does not fit even the imperfectly known clinical or pathological characters of the disease. The confusion is recognized by Klinger, Arkin and others who have suggested distinguishing features. This report is a further attempt at clarification. The arterial diseases described below have been found sometimes in single organs or parts, sometimes in a few separate situations and sometimes widely distributed. In this study attention is directed particularly to small arteries of different size, generally with an outside diameter of something in the order of 100 to 500 micra and not

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From The Institute of Pathology, Western Reserve University and University Hospitals, Cleveland, Ohio.

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† In the literature the terms necrosing and necrotizing are used interchangeably. The latter has become customary in this laboratory.

including arterioles with an outside diameter of 50 micra or less. The inflammations occupy usually only a comparatively short segment of the vessel. They do not frequently extend to the arterioles and if they do, they involve only the proximal part of the arteriole.

In order to facilitate discussion, a classification is desirable and the following scheme is suggested.

ARTERITIS

Acute
- Alterative (degenerative)
- Necrotizing
- Exudative
- Vegetative (thrombo-arteritis)
- Proliferative
- Organizing

Chronic—combinations of
- Intimal
- Medial
- Adventitial

Acute Alterative (Degenerative) Arteritis. The simpler retrogressive changes are found principally in the form of intracellular and intercellular edema. Lesions of this sort were described as early as 1869 by Hayem as an accompaniment of infectious diseases. The intima may show swelling not only of the endothelial lining cells but also those of the sub-endothelial

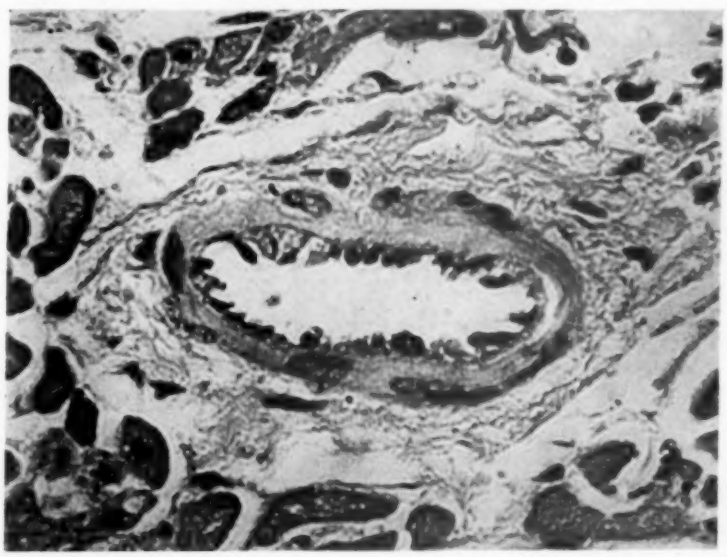

FIG. 1. Edema of media, observed as a vacuole at one pole of section, together with granularity of cytoplasm and almost complete disappearance of medial nuclei. Acute degeneration. Male, aged 5 years, rheumatic fever. (× 500.)

tissues in arteries of sufficient size to have this layer. Intercellular accumulations are not frequent but may be observed, especially in rheumatic fever. The media may show the same forms of disease. So-called chromotropic degeneration is found much more often in the media than in the intima. It differs from simple edema in that it stains somewhat as does connective tissue mucoid, but is probably primarily edematous in character. Changes in the elastic laminae include swelling, splitting and fragmentation. The justification for regarding these degenerative lesions as inflammatory lies not in the fact that they invariably show associated exudative or proliferative phenomena, but rather in that they exhibit these changes as the disease progresses. This progression is indicated by comparison of a large number of specimens rather than by directly observed sequences.

In addition to the infectious diseases, vascular edema has been observed in neo-arsphenamine poisoning (Christianson), in experimental allergy (Murasawa, and Kaiserling and Ochse), following partial denervation (Kerper and Collier), as the result of repeated grafting of adrenals (Leriche and Froehlich), and as a result of prolonged life in compressed air (Smith, et al.). Both edema and chromotropic change are common in periarteritis nodosa.

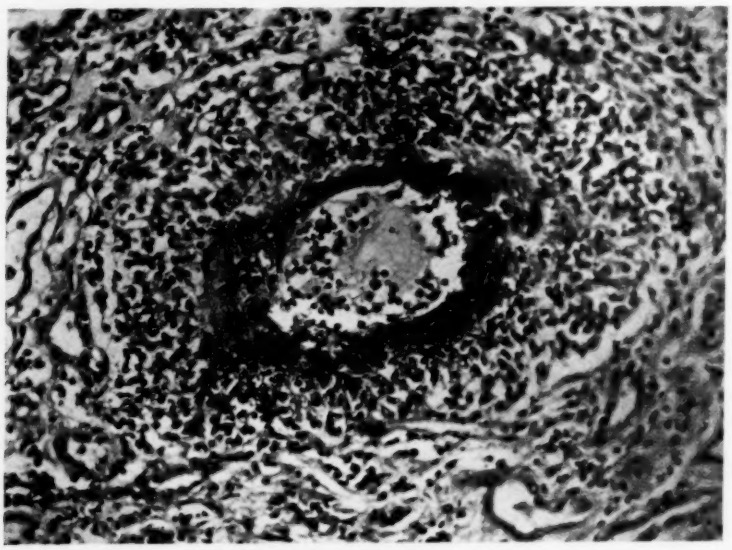

FIG. 2. Acute necrotizing arteritis in kidney. Unexplained acute diffuse arterial disease. Female, aged 19 years. (× 194.)

Acute Necrotizing Arteritis. Except where a lesion is found in arteries which are so small that they approach arteriolar size, necrosis generally is first seen in the media. It may occur as an isolated area but usually involves the entire circumference of the artery in a given segment. Confluence of cells, coarse granularity or hyalinization of cytoplasm and complete dis-

appearance of nuclei usually characterize the necrosis. With the exception of minute arteries, pyknosis and karyorrhexis are only occasionally present. Necrosis often extends to involve the intima and adventitia, but except for the smallest arteries is rarely primary in those coats. In contrast to the simpler degenerative lesions, exudation is constant when necrosis is found. The proportions of the cells of the exudate vary; sometimes they are principally lymphocytes and sometimes the polymorphonuclear leukocytes predominate. Lesions of this sort are observed in experimental anaphylaxis or allergic states (Kaiserling and Ochse, Ssolowjew and Ariel, Eickhoff), as the result of injections of trypan blue (Pfuhl), following injections of specific antisera (Matsugi et al.), in the Shwartzman phenomenon (Karsner and Moritz), following injections of allylamine (Mellon, Baker and McElroy), and other procedures. In man the necrotizing lesions are occasionally found in infectious diseases, especially those with septicemia; they occur in rheumatic fever and are well shown in the skin of erythema induratum.

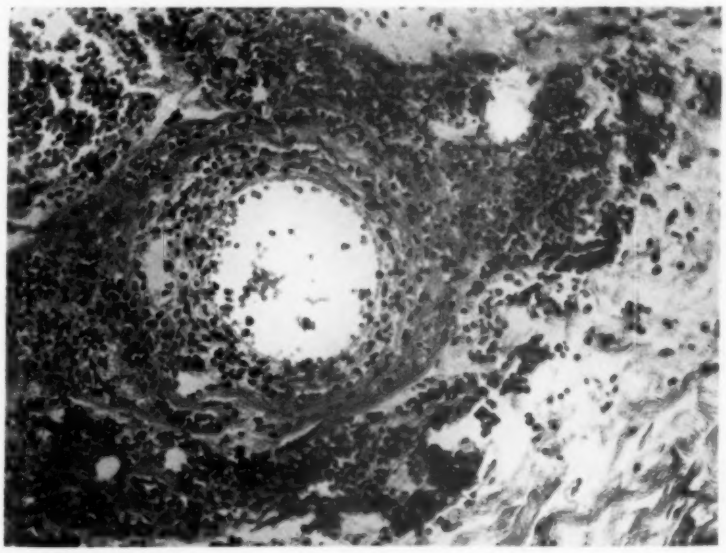

FIG. 3. Acute exudative arteritis, with hemorrhage. Erythema induratum. Female, aged 19 years. (× 194.)

Acute Exudative Arteritis. The term exudative includes both cellular and fluid exudation. The fluid can be determined to be exudative anatomically only by the presence of fibrin. Cellular exudation may be present without deposition of fibrin and if both be present the cellular component predominates, but occasionally the fibrin may form a conspicuous part of the exudate. Lesions of this sort are found especially in secondary arteritis, but are not infrequent among the primary forms. Exudation accompanies other changes such as degeneration, necrosis and cellular pro-

liferation. It occurs in a wide variety of conditions including some of the cases of rheumatic fever. The combination of necrosis and exudation, a necrotizing-exudative arteritis, characterizes the acute stages of periarteritis nodosa, and occurs in the conditions noted in the preceding paragraph.

Acute Vegetative (Thrombo-) Arteritis. Although it may be true, as claimed by Nygaard and Brown, that thrombosis can occur without disease of the intima or other coats of the vessel, the deposit of thrombi usually follows other arterial lesions. Thrombosis is common to the more severe arterial inflammations and also occurs in arteries where the inflammation

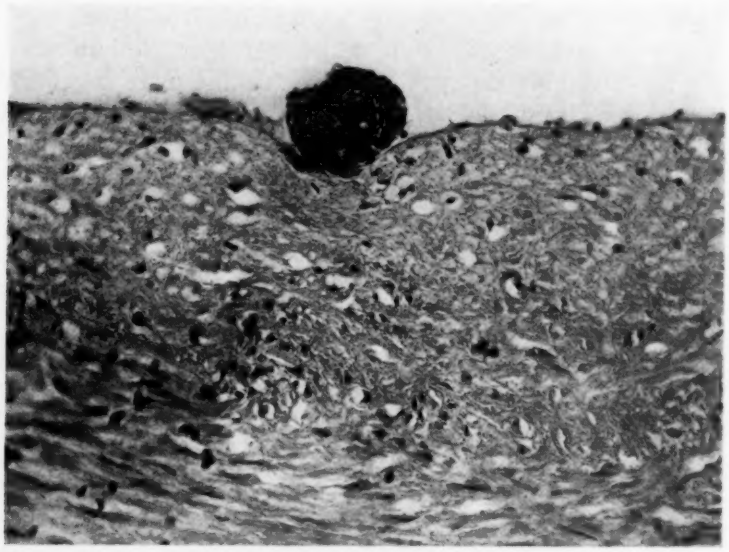

FIG. 4. Acute vegetative arteritis. Thrombus attached to wall of a large coronary artery. No bacteria. Male, aged 24 years. Rheumatic fever. (× 226.)

or degeneration can be identified anatomically only as the result of careful study. The deposit of fibrin may start in the intima or upon the intima and may be of focal form, resembling vegetations, or occlusive. Other phenomena of inflammation are frequently found. The resemblance of this form of arterial disease to endocarditis has been emphasized by Baehr, Gross, Bender, Matsugi and others. It would appear that in the arteries, as in the endocardium, the primary lesion is subintimal and the thrombus formation secondary. In those cases in which endocardial disease is present, there may be emboli into the arteries, but thrombo-arteritis occurs without associated endocarditis and can be considered to be an independent phenomenon. In some instances it may be due to deposit of bacteria from the blood stream, a secondary inflammation, but that primary forms exist is confirmed by their occurrence in patients without bacteremia and without demonstrable bacteria in the thrombus.

Acute Proliferative Arteritis. Proliferation of cells in acute arteritis is observed almost solely in the intima. There are cases in which this is undoubtedly a proliferation of endothelial cells. In many, however, masses of swollen mononuclear cells with poorly staining cytoplasm, of uncertain origin, form masses piled up into the lumen of the artery. Thrombosis is not found except as a later manifestation and exudative cells are found not so noticeably in the intima as in the adventitia. Even in the latter situation, exudation may be scanty. Intimal proliferation is seen in many varieties of arteritis such as that observed in rheumatic fever, in syphilis and cases of more or less localized arteritis without known cause. It is reported

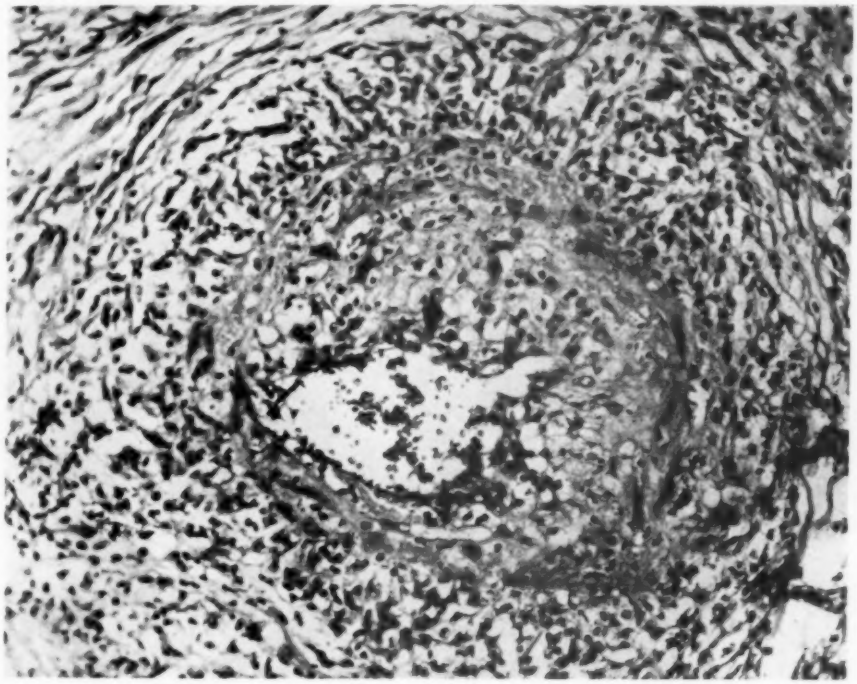

FIG. 5. Acute proliferative arteritis. Disease localized to region of gall-bladder and kidney. Female, aged 35 years. (× 190.)

by Wiese in pulmonary thrombo-arteritis, by Leriche and Froehlich in the arteritis following adrenal grafting, and by Kaunitz and by Yater and Cahill in ergotism. It may be found sometimes in periarteritis nodosa. It is reasonable to assume that as endothelial proliferation in glomerular capillaries signifies an inflammatory reaction, this lesion of arteries may be similarly interpreted. Proliferation of medial connective tissue cells, of fibroblastic type, as an indication of acute reaction is uncommon but may be found, especially in the florid stages of rheumatic fever.

Organizing Arteritis. This is observed as a later stage of arteritis, particularly that which has been associated with thrombosis. The character

of the granulation tissue is not different from that observed elsewhere, except that as organization proceeds it is likely to be accompanied by canalization. Buerger considers the later vascular lesions of thromboangiitis obliterans to be an organizing stage of a previous acute thrombo-arteritis.

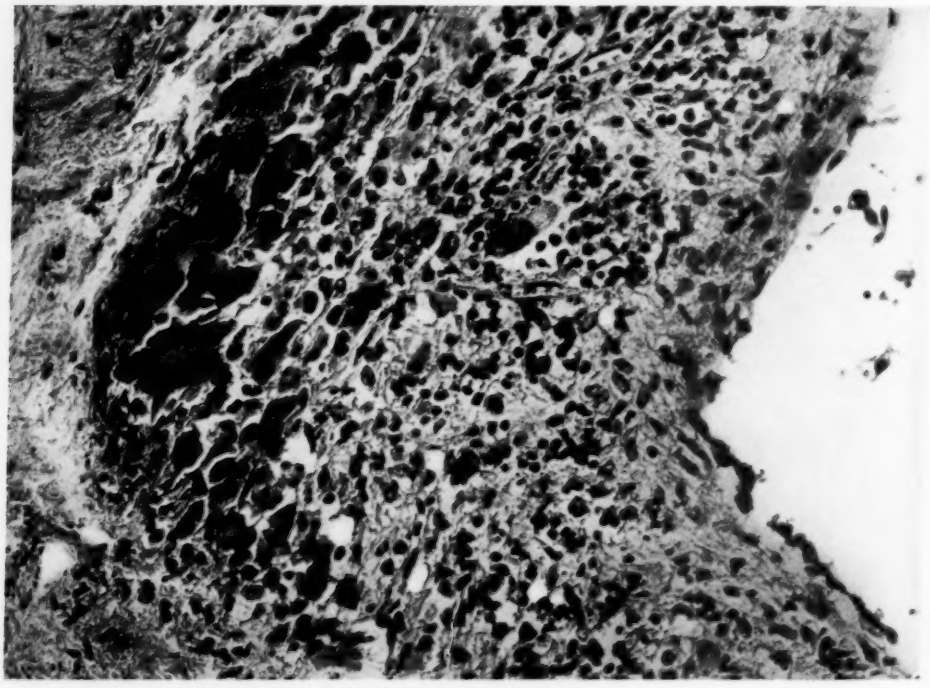

FIG. 6. Organizing acute arteritis. Epicardial artery of a case of periarteritis nodosa. Female, aged 26 years. (× 300.)

Wiese describes it in primary pulmonary thrombo-arteritis. It is well seen in periarteritis nodosa and in other diseases where survival permits of organization.

Chronic Arteritis. In this category are included progressive fibrotic disease of arteries, which do not show the lipoidosis, atheroma or calcification of arteriosclerosis. This differentiation cannot be considered inflexible because any dense fibrous mass may finally become fatty and calcified. That it is progressive, as required by definition of chronic inflammation, is assumed by the variation in the appearance in different arteries from the same patient. Only occasionally does it show lymphocytic infiltration. It differs from endarteritis obliterans, intimal arteriosclerosis and the senile medial disease of Mönckeberg in that it involves two or more coats and when it occurs in the media is irregularly distributed and does not show calcification. It is particularly well illustrated in rheumatic fever, where the chronic arterial lesion resembles the chronic endocarditis. It occurs in

thromboangiitis obliterans. It is seen in the smaller arteries, such as the vasa vasorum in syphilis. That this form of syphilitic disease is due to the direct action of spirochetes is doubtful, because they are not demonstrable in the lesion.

On the basis of a single preparation it is often impossible to distinguish chronic arterial inflammation from involutional changes such as are observed in the senile uterus, ovary and other situations. The same may be true of destructive and reparative phenomena in such lesions as chronic cholecystitis. These difficulties are ameliorated if specimens from many parts of the body be available for study.

Discussion

The material upon which this classification is based was from patients who presented a wide variety of clinical manifestations. Extensive acute arteritis may express itself with fever, leukocytosis, purpura and similar general phenomena. If localized, as for example in the gall-bladder, kidney or appendix, etc. (Plaut), the clinical features disclose the localization and general signs depend upon the severity of the disease. As with arteriosclerosis of medium sized and small arteries, the immediate effects of acute arterial inflammations are referable to the effects within the parts diseased, but acute arteritis differs in that it presents more or less marked signs and symptoms of a general disease. In one case of acute proliferative arteritis of kidney and perirenal structures, surgical removal of the diseased tissues resulted in apparently complete recovery as long as the patient could be traced (four years). In contrast, a case of chorea in a child resulted in death in a few weeks with widespread acute exudative arteritis, of rheumatic character. Chronic arteritis is without accompanying clinical signs unless it be of sufficient degree to produce local atrophy and fibrosis with resultant physiological change, as is also true of arteriosclerosis. These statements are in accord with the distribution and character of the lesions as outlined in the introductory paragraphs.

The acute lesions described rarely occur as pure forms. The combination of necrosis and exudation is worthy of special comment because this is the lesion seen most often in periarteritis nodosa. In the typical cases the cells of the exudate include eosinophiles, both polymorphonuclear and mononuclear. Arkin did not consider the eosinophile as an essential feature. Middleton and McCarter mention eosinophilia of the circulating blood but do not emphasize eosinophiles in the exudate. There is no mention of these cells in the reports of Bennett and Levine, of Yardumian and Cohen, or of Krahulik, Rosenthal and Loughlin. Friedberg and Gross note the eosinophiles in one of their four cases and Curtis and Coffey, Bernstein and also Dungal in each of their cases. Gruber, who suggested discontinuous hypergic phenomena as the cause of the disease, paid little or no attention to eosinophiles, whereas Kline and Young suggest that the local eosinophilia

supports the hypothesis of allergic causes. Certainly a necrotizing-exudative arteritis occurs both in man and experimental animals without the general manifestations of periarteritis nodosa. While it would perhaps be too stringent to insist upon the finding of eosinophiles to establish the diagnosis, the local eosinophilia should be given a place of great importance. As emphasized by Klemperer, there are other features of significance if the original meaning of the term periarteritis nodosa is to be preserved, as for example, the presence of nodules visible to the naked eye or through the hand lens as well as the microscopic demonstration of aneurysms. With the criteria suggested, it should be possible to avoid the conclusion that a wide variety of acute arterial inflammations belong in the category of periarteritis nodosa.

Syphilitic disease of smaller arteries, especially those of the meninges, is characteristically exudative and necrotizing. Because spirochetes have not been found in the lesion (Spielmeyer), it has been thought to be due to "toxins." In a recent case observed in this department, spirochetes were found in abundance. Thus, this form of syphilitic arterial disease belongs in the proposed category of secondary arteritis, as is true of tuberculous arteritis and other forms, as for example that seen in typhus fever, hog cholera, brucelliasis, etc.

In human material, involvement in variable degree of all the coats of the artery is usually found, although often the lesion is especially conspicuous in one or another of these layers. Thus it might be assumed that the inflammation begins in the entire wall as a unit. That this assumption is probably not valid is indicated by the experiments of Ramsey and her coworkers, who found that chemical, particulate or bacterial injury of the intima is first reflected in reaction in the perivascular tissues (adventitia and surrounding connective tissue) or the outer portions of the media. Exudation then extends through the media, appears to be temporarily hindered by the internal elastic lamina, but soon involves the entire wall. Thus it would be unwise to suppose that because a section of artery shows a given lesion to be especially prominent in one coat, that coat is the one primarily affected. The course and sequences of arteritis deserve extensive and detailed study.

Summary

In addition to those inflammations of arteries of small and medium size due to extension of local inflammation or direct invasion of bacteria and other organisms, which may be designated as secondary arteritis, there are forms of arteritis due to unknown or ill-defined causes which can appropriately be named primary arteritis. The lesions found in these primary forms have been classified and include both acute and chronic varieties, the former varying from degenerative and necrotizing to exudative, proliferative and organizing forms. The chronic forms differ from arteriosclerosis in distribution of fibrosis in the three coats of the arteries and by delayed or ab-

sent secondary changes in the fibrous tissue. It is suggested that an improved nomenclature for the varieties of arteritis will aid in correlating descriptive morphological and clinical data so that a precise understanding of these diseases will be attained.

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AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR OF DOCTOR JOSEPH HERSEY PRATT

HEALED BACTERIAL ENDOCARDITIS *

By Louis Hamman, F.A.C.P., *Baltimore, Maryland*

If we base our views about the course of subacute bacterial endocarditis solely upon routine observations made in the clinic, we must conclude that it is an exceptionally malignant disease, for almost invariably it ends in death. Reckoned from the time symptoms first appear the average duration of the illness is about six months and only seldom does the affected patient live longer than a year. In 1924 Thayer reported that of 206 cases, collected from the records of the Johns Hopkins Hospital, none had recovered. As far as I know the uniform mortality of the disease at that hospital has not changed during the past 12 years, for I am convinced that had a recovery occurred, this exceptional event would have been loudly proclaimed, and could not have escaped my notice. Certain I am, that no well-established instance of subacute bacterial endocarditis, which has been under my observation, has ever recovered. This depressing experience is by no means unusual, for many seasoned practitioners tell me that their results have been precisely the same. I think it is true that when the diagnosis of endocarditis lenta is securely made then most physicians regard the outcome as hopeless.

Nevertheless, in spite of this almost universal pessimism, it cannot be doubted that occasionally recovery does occur. However, not so frequently as is reported in the literature, for a careful examination of these reports reveals that in many the diagnosis has not been conclusively established. In some the blood cultures have been sterile; in others the evidence of an endocardial lesion is unconvincing; in still others the facts are so incompletely reported that it is impossible to identify the true nature of the illness. Many competent observers in discussions and under other circumstances merely state that in their experience so many patients have recovered without giving any clinical details. Knowing the established reputation of these physicians one cannot doubt the accuracy of their statements even in the absence of supporting facts. However, leaving all these reports aside, we may still find detailed and convincing accounts of many cures. I do not pretend to name them all but choose as illustrations those instances reported by Murray, Hemsted, Capps, Bogendörfer, Schottmüller, Perry, Kissling, and Kraiss.

I have omitted from this list the name of Libman because his reports contrast so violently with general experience that they must be noticed separately. Libman reports at least 3 per cent of recoveries in the usual

* Presented at the St. Louis meeting of the American College of Physicians, April 20, 1937.

type of the disease and is convinced that many more recoveries occur in mild cases which are often overlooked. He publishes brief notes of 17 recovered cases, some dying in a second or even third attack after intervals of many years. I must admit that Libman's results are more in accord with evidence obtained post mortem than are the usual results of other physicians. This is strong corroboration of the truth of his observations, if, indeed, any corroboration is needed for the observations of so distinguished a student in this field. Therefore it is interesting to ask what may be the reason for the divergence of these results.

The characteristic clinical symptoms of subacute bacterial endocarditis are fever, anemia, evidence of a valvular defect or a congenital abnormality, splenic enlargement and embolic phenomena. When these symptoms are well developed the diagnosis is assured. However, very often one or more of the symptoms is absent and then the diagnosis may be difficult. For instance, when there are no embolic phenomena, the disease, in its mild forms, may very closely resemble rheumatic fever. Indeed, often it is impossible to distinguish confidently between them. It is unnecessary to remind you how very difficult it is at times, even in the presence of loud murmurs, to be sure that there is an endocardial lesion; and yet without this confidence one can only surmise, but never state, that the patient has bacterial endocarditis.

The diagnosis of bacterial endocarditis can be made without actually demonstrating the presence of bacteria in the blood stream although this demonstration is always desirable and under circumstances, when the complete clinical picture is not developed, it is essential. However, it must be emphasized again and again that the mere presence of bacteria in the blood stream, when other characteristic symptoms, especially the undoubted presence of an endocardial lesion, are absent, does not warrant the diagnosis of subacute bacterial endocarditis. On many occasions pyogenic organisms gain access to the circulating blood but do not settle within the heart and the presence, say, of staphylococci in blood cultures and of a systolic murmur over the heart does not justify the diagnosis of bacterial endocarditis, especially not, if the observer reports that an examination made months later, when the patient had recovered, demonstrated the heart to be normal. It is now common knowledge that the *Streptococcus viridans,* the organism most often concerned in subacute bacterial endocarditis, frequently invades the blood stream when there is infection in the upper respiratory tract and no doubt less frequently with infections located elsewhere. Therefore, the presence of bacteria in the blood during the course of a febrile reaction does not signify that the endocardium has become infected, unless at the same time there is undisputed evidence of a valvular lesion or a congenital defect, and other characteristic symptoms of bacterial endocarditis are present.

Whether the remarkable groups of cases reported by Oille, Graham and Detweiler, of Toronto, and by Salus, of Prague, are real instances of

Streptococcus viridans endocarditis or instances of bacteremia without endocarditis is difficult to decide. Certainly, their experience is unique, and I can only say for myself, that to me the evidence upon which is based the diagnosis of endocarditis is unconvincing. Oille, Graham and Detweiler report an epidemic of 23 cases, mostly in children, observed during a period of six months. The constitutional symptoms were mild; fever slight or absent; there were no embolic phenomena; all recovered. The evidence of endocardial involvement consisted almost entirely of apical and aortic systolic murmurs. Only three showed slight enlargement of the heart. Blood cultures in all were positive for *Streptococcus viridans* but only one culture was taken in 17 of the cases. These results contrast with the report of Warren and Herrick who collected from the records of the Roosevelt Hospital 134 cases with positive blood cultures. In 40 the infecting organism was the *Streptococcus viridans*. Twenty-five of the 40 had endocarditis; of these 22 had died, three were still living but unimproved. Of the remaining 15 cases, without endocarditis, 10 had recovered.

It is reasonable to assume that instances of bacterial endocarditis with very mild clinical symptoms are the ones which have the best chance of recovery. Moreover, this assumption is strongly supported by postmortem observations. However, it is these mild cases which are particularly difficult to recognize. Often there is but little fever; anemia, though always present, may be slight; and appreciable splenic enlargement and embolic phenomena may be absent. Usually they are regarded as instances of rheumatic or syphilitic heart disease and the autopsy revelation, demonstrating bacterial endocarditis, comes as a great surprise. With experience, the diagnosis of bacterial endocarditis may often be proposed under these circumstances, but cannot definitely be made, unless cultures demonstrate repeatedly the presence of bacteria in the blood. Unfortunately, in these mild cases, only a small number of bacteria may be washed into the blood stream and undoubtedly, sometimes, they are present there only interruptedly. Therefore, to recover them cultures must be made repeatedly and with great care. I cannot say to what degree technical skill in bacteriology may improve the diagnosis of these mild cases. As regards the gonococcus I am sure that success in cultivating it from the blood stream depends in large measure upon the experience and skill of the investigator. The gonococcus is often the infective agent in these mild cases of bacterial endocarditis and yet, although it is usually recovered from fulminating cases of the disease, it is very seldom demonstrated in the mild cases. Nevertheless, the conditions found at autopsy indicate plainly that during life many bacteria must have been discharged into the blood stream. As regards the *Streptococcus viridans* there is not the same difficulty in growing it. The methods are now standardized and with reasonable care should give uniform results. However, it is always possible that extraordinary care may be more often successful. It is a matter worthy of consideration.

Let it be understood that nothing is further from my intention than to explain, as due alone to imperfect or faulty technic, the well-known fact that it is usually difficult and often impossible to grow bacteria from the blood of patients with mild and protracted symptoms of bacterial endocarditis, even when the conditions found at autopsy demonstrate clearly that large numbers of bacteria, constantly or intermittently, must have escaped into the blood stream. As I have already remarked it is usually a very simple matter to recover bacteria from the blood of patients acutely ill. The difficulty arises only when the disease is mild and of long duration. This difference, I think, must depend chiefly upon the gradual development of immunological forces. When, with the passage of time, the body acquires a powerful system of defense, then, although bacteria are swept into the blood stream, they are immediately attacked and soon destroyed. There is abundant evidence of the efficiency of this mechanism. The very fact that suppuration so seldom occurs is difficult to explain upon any other assumption. Even when the infective agent is the *Staphylococcus aureus,* widely spread abscesses are seldom seen in subacute cases. Occasionally we are successful in growing organisms from the blood drawn by puncture from the brachial artery, whereas, repeated efforts to grow them from venous blood are unrewarded. Here we may suggest that many bacteria are removed from the blood during its passage through the capillaries, but it seems to me even more likely that the fact is due to the greater length of time allowed the forces of immunity to play upon the bacteria. The apparent contradiction that in the face of these destructive forces bacteria still grow freely upon the infected valves is explained simply by the location of the bacteria, a location which shields them safely from harm. If you will look upon the stained section of an infected valve you shall see that the bacteria are accumulated beneath the margin of the valve where no blood vessels penetrate, and where they are secure from the reach of injurious chemical substances in the blood which bathes the valve, and from attack by leukocytes which may settle upon its surface. From this sheltered home colonies wander out towards the base of the valve but they do not penetrate far, for when they reach the area supplied by blood vessels they quickly perish.

I can propose only three possible explanations for the unusual results which Libman reports. First, being especially interested and experienced in the diagnosis of bacterial endocarditis he recognizes many mild cases which would escape the notice of average observers. Second, he is more indefatigable in the search for bacteria in the blood stream. Third, his technical resources in bacteriology are superior to those of the average laboratory.

When now we turn from the clinical experience with bacterial endocarditis and regard the disease from the standpoint of the pathologist we shall see prognosis in a different light. I think the pathologist, entirely unacquainted with the clinical course of the disease, and basing his opinion

solely upon what he observes at the postmortem table, would be surprised to hear that very few patients recover. In all but the very acute cases he is accustomed to find unmistakable evidence of healing. In one case, although there are active vegetations along the margins of a valve, in other portions dense fibrosis and calcification show where previously active lesions have healed. In another case, the process is mildly active upon one valve, whereas, another valve is scarred and contracted showing no longer vegetations or bacteria. In still another case, there is scarring and calcification of one or more valves without the slightest remaining evidence of infection, only the scarred remnants of infection long past. In a word, he sees almost regularly a strong tendency to healing; not infrequently a state of affairs where healing has become nearly complete so that he remarks, "if the patient had lived a little longer surely he would have recovered"; and occasionally only stiff fibrotic valves as evidence that a previous lesion has completely healed.

The object of this communication is to attempt to bring our clinical and pathological experience more nearly into accord. This has been done before, for instance, by Libman and by Weiss and Rhoads. Still I think the subject is worthy of repeated attention. Those who are accustomed to follow patients from the ward to the postmortem room soon become convinced that in the clinic they fail to recognize many cases of bacterial endocarditis, and, from the character of the lesions there observed, that many patients recover and then live on for years with the usual evidence of a valvular defect. To illustrate these facts I have selected a few recent observations.

Case I

L. B., 29 years, female, colored, single.

A colored housemaid, then 27 years of age, came to the Gynecological Clinic of the Out-Patient Department of the Johns Hopkins Hospital on February 9, 1932, complaining of pain in the abdomen and too frequent menstruation. The diagnosis was made of right-sided, chronic inflammatory pelvic disease and myomatous uterus. She returned to the Medical Clinic of the Out-Patient Department on January 30, 1933, complaining of palpitation of the heart and shortness of breath. Two days later she was admitted to the hospital. There she stated that she always had been well, except for the menstrual disorders for which she had gone to the Gynecological Clinic, until December 27, 1932, when she was taken during the night with severe pain about the umbilicus. Later she had pain on the left side of the chest which persisted for three days and then disappeared. This pain was severe and was increased by deep breathing. During the attack the patient had nausea and vomited on several occasions. When these symptoms came on the patient had had for some days a slight cold. After the attack of pain she had cough, with a little expectoration, which at times was spotted with blood. She was quite sure that she had had fever. After the attack she was up and about for a few days but she then began to notice that she was very short of breath and that the heart beat rapidly and forcefully on slight exertion. The shortness of breath grew steadily worse and soon she was unable to lie down in bed. After 10 days her symptoms improved somewhat and she tried to work, but immediately became so short of breath that she had to give it up. She then noticed that her ankles were swelling and that palpitation and weakness were growing more pronounced.

Examination. Temperature, 100.2°; pulse, 102; respirations, 48; blood pressure, systolic 90, diastolic 60.

The patient was a well-developed, poorly nourished colored woman, propped up in bed, breathing rapidly but not in great distress. There was no cyanosis and no edema other than a little pitting over the shins. She evidently had lost weight. The mucous membranes were rather pale. The eyes were normally prominent, extra-ocular movements well performed. Pupils were equal, reacted actively to light. The fundi showed no abnormality. The teeth were in poor condition with marked pyorrhea. The pharynx was slightly injected; the tonsils were enlarged and scarred. Glands at the angles of the jaw were somewhat enlarged. Otherwise there was no glandular enlargement. The thyroid was just palpable. Trachea was in the midline.

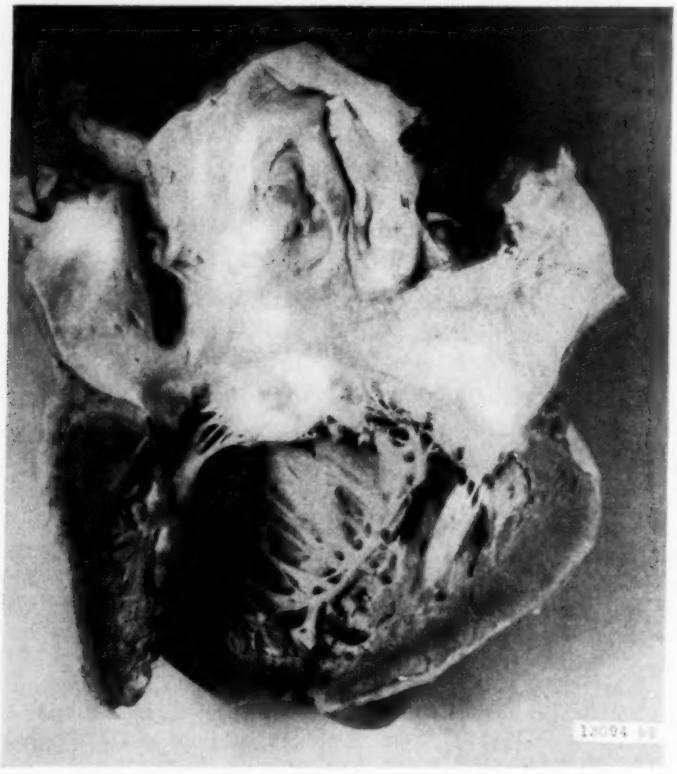

FIG. 1. Heart of Case 1. For description see text.

The chest was well formed and symmetrical. The lungs showed no abnormality other than a few moist râles at the right base. The heart was greatly enlarged. There was a diffuse forcible impulse all over the precordium. The apex beat was in the fifth interspace, 11 cm. from the midline. At the apex the shock of the first sound could be felt and at the base the shock of the second pulmonary sound. At the apex there was also a presystolic thrill. The area of cardiac dullness measured 5½ cm. to the right, and 12 cm. to the left of the midline. At the apex the first sound was loud and booming in quality; it was immediately preceded by a short rumbling presystolic murmur, and was accompanied and followed by a loud, harsh systolic murmur, widely transmitted. It was well heard in the axilla and below the angle of the scapula in

back. The second pulmonary sound was greatly accentuated. Rhythm was irregular due to the occurrence of very numerous extrasystoles. The pulse was soft, rapid and of small size. The vessel walls were not thickened. The abdomen was normal in appearance; the walls were soft and relaxed; no tenderness; no masses were felt. The edge of the liver was 3 cm. below the costal margin; it was slightly tender. The spleen was not enlarged. The pelvic examination revealed a myomatous uterus. The rectal examination was negative. The neurological examination was negative.

Course in the Hospital. After a period of rest with digitalis, the patient rapidly improved and at the end of six weeks was up and about the ward in comfort.

Laboratory Examinations.

Blood Count: 2/1/33. Hgb. 54 per cent; R.B.C. 3,550,000; W.B.C. 8,900.
3/18/33. Hgb. 72 per cent; R.B.C. 4,700,000; W.B.C. 9,600.

Wassermann reaction was strongly positive.

Blood Culture: 2/10/33. No growth.

Lumbar Puncture: 3/7/33. 10 c.c. clear, colorless fluid withdrawn. No evidence of increased pressure. No cells. Pandy negative. Wassermann reaction negative. Colloidal mastic test negative.

Urine: Specific gravity varied from 1.014 to 1.030. Occasionally there was a trace of albumin but usually none. The sediment contained a few pus and epithelial cells.

The temperature on admission varied from 99° to 100.4°. On February 23 it rose to 102° following the extraction of an infected tooth. Subsequently it fell again, ranging between 98.6° and 100°.

The pulse rate varied from 70 to 110.

Roentgenogram: 2/2/33. Tele.: M.R. 6.8, M.L. 10.3, A. 4.5, T. 27.3.
The heart is very much enlarged. Changes in the lungs are secondary to the cardiac condition.

Electrocardiogram: 2/7/33. Normal sinus rhythm. T_3 inverted. There is a shift of 21 degrees of the electrical axis on change of position.

Course after Leaving Hospital. The patient left the hospital on March 18, 1933, and was referred to the Syphilis Clinic for treatment. She reported there on March 23 and received an injection of bismuth. She was comfortable for only about one week after discharge when the shortness of breath returned. Apparently this was inaugurated by a cold. She was hoarse and had cough with mucopurulent expectoration. After this the shortness of breath grew worse and edema again appeared. She entered the hospital the second time on March 21, 1933.

Examination. Temperature, 100°; pulse, 90; respirations, 26; blood pressure, systolic 90, diastolic 62.

Examination on this occasion showed essentially the same conditions reported on the first admission. Dyspnea was not intense, she could lie flat without becoming short of breath. There was no cyanosis. The edema was somewhat more marked than on the first admission; there was pitting over the tibiae and over the sacrum. The liver also was more markedly enlarged, extending to the level of the umbilicus. On this occasion the pulse at times was regular, at other times there were numerous extrasystoles, and on still other occasions, for brief periods, there were paroxysms of fibrillation.

Course in the Hospital. (Second Admission.) The patient was given digitalis. She became nauseated and vomited frequently. Later theocin was given. This seemed also to bring on nausea. Although on admission the patient's condition was far from desperate, she grew progressively worse. The heart seemed gradually to enlarge, certainly it was larger than during the first admission. Numerous râles were heard over the lower lobes of both lungs and signs soon developed suggesting a small pleural effusion on the right. Breathing became more and more difficult.

The peripheral veins were greatly engorged and the patient became cyanosed. On April 7, 1933, eight days after her second admission to the hospital, she suddenly died.

Laboratory Examinations.

Blood Count: 3/31/33. Hgb. 62 per cent; R.B.C. 3,200,000; W.B.C. 15,800.

Urine: Specific gravity varied from 1.020 to 1.030. There was a trace of albumin. A small number of pus cells and a few R B.C. in the sediment.

Electrocardiogram: 4/6/33. Normal sinus rhythm. P–R interval 0.22 sec. P-waves broad and notched in all leads. T_3 inverted. Sinus tachycardia.

The temperature ranged from 99° to 101°.

The pulse rate ranged from 80 to 120.

The clinical diagnosis made upon the hospital ward was rheumatic heart disease; mitral stenosis and insufficiency. However, a number of observers suggested the possibility of bacterial endocarditis and when, after death, the case was finally discussed at the clinical-pathological conference, the diagnosis of bacterial endocarditis was preferred. That this diagnosis was not seriously considered during life is demonstrated by the fact that only one blood culture was taken. In addition to the clear evidence of a mitral valve lesion, anemia and a low-grade fever were conspicuous elements of the clinical features of the disease. This made it certain that the patient must have had either an active rheumatic infection or bacterial endocarditis. The rapid course of the disease was the peculiar feature which led finally to the acceptance of the diagnosis of bacterial endocarditis. From the very first onset of symptoms, on December 27, 1932, to the date of death, April 7, 1933, was a period of only a little over three months, and although improvement occurred while the patient was in the hospital, carefully treated and solicitously shielded, still, the improvement was very superficial, for only one week after leaving the hospital severe symptoms returned and shortly thereafter she died. What a contrast this is to the usual course of rheumatic heart disease. Very seldom does the rheumatic patient fail to improve satisfactorily during the first attack of heart failure, and usually, long periods of relative comfort separate recurring attacks.

The postmortem examination revealed the characteristic lesions of bacterial endocarditis. The striking feature of the lesions was the advanced healing which had taken place. The valves were thickened and fibrous, in places calcified; the vegetations consisted mostly of hyalin masses and some were undergoing rapid organization. Here and there on the surface were crops of bacteria. These were gram-negative cocci, in all probability gonococci, although they did not grow in cultures and therefore could not positively be identified. There was no evidence of active or preëxisting rheumatic disease. The valvular infection seemed to be a primary one, due to the gonococcus.

Brief notes from the autopsy report are as follows:

Anatomical Diagnosis: Subacute bacterial endocarditis involving the mitral valve (gram-negative cocci) transplantation on intraventricular septum. Hyaline vegetations on auricular endocardium; hypertrophy of left ventricle of the heart; chronic

passive congestion of lungs and liver; infarction in spleen; thrombosis of pelvic veins; pulmonary emboli; fresh pulmonary infarcts; pulmonary edema and lobular pneumonia; myomatous uterus; chronic bilateral salpingitis; intraperitoneal adhesions.

Dr. F. B. Kindell's note on the heart: The heart is enlarged, weighing 480 grams. The surface of the right auricle shows areas covered by tough little granules of organized exudate. There are punctated hemorrhages beneath the epicardium of the right ventricle. The right ventricle is a little hypertrophied. The tricuspid and pulmonary valves are thin and delicate. The left auricle is moderately dilated. There is a roughened patch in the auricular endocardium some distance above the mitral valve. Some of these thickenings are old and smoothly covered by endocardium; other little patches are made up of tiny granules which are tough and some are suggestively gritty. The mitral valve is thickened. The margins of the leaflets are gray and fibrous. The change is most marked along the edge of the aortic leaflet. There are also fresher greenish-gray vegetations along the line of closure but they are most pronounced along the chordae tendineae which are attached to one wing of the aortic leaflet. Most of these are broken. The larger masses of vegetations are distinctly tough, apparently partly organized. The marginal fringes are softer and crumbly. Three centimeters below the aortic orifice there is a granular patch suggesting partly healed vegetations on the endocardium of the interventricular septum. This is precisely in the position where the flapping loose ends of the chordae tendineae must have brushed the ventricular wall. The aortic cusps showed no lesions. The aorta, except for fine streaks of fat, has a normal intima. The larger branches of the coronary arteries are normal.

Microscopical Report: The mitral valve is quite thick and fibrous. In the small section which shows the fresher vegetations it is found that these also are of some duration. The center of the mass is calcified and it is only on the surface that crops of bacteria are found. These are gram-negative cocci, somewhat smaller than gonococci generally are. The lesion from the interventricular septum shows a thickened endocardial layer with rather numerous scattered mononuclear cells. The vegetations on the surface are hyaline. The lesions from the lining of the auricle are quite fibrous but there are hyaline masses on the surface. There are only a few minute scars in the myocardium and on the whole there is little support for the view that the older thickening of the mitral valve and the hyaline lesions in the auricle were originally rheumatic.

Case II

J. C., 51 years, male, colored, married.

A colored laborer, then 48 years of age, came to the Medical Clinic of the Out-Patient Department of the Johns Hopkins Hospital December 15, 1933, complaining of pain in the lower part of the abdomen and shortness of breath. At 19 years of age he had had an attack of rheumatic fever lasting three months. This had come on after exposure. All of the joints had been involved and were swollen and inflamed. Ten years before admission he had had an attack of sciatica in the left leg and following this he had had six or eight recurrent attacks. He said he never had had either gonorrhea or syphilis, although he described symptoms that made it almost certain that he had had a gonococcus infection at 18 years of age. In other respects he had been a healthy man, working hard until three weeks before coming to the Out-Patient Department. At that time he had had pain in the lower part of the abdomen soon followed by shortness of breath. The pain in the abdomen was described as a dull soreness. The shortness of breath progressively had gotten worse and for some nights before coming to the hospital he had been unable to lie down.

Examination. Temperature, 98°; pulse, 96; respirations, 20; blood pressure, systolic 160, diastolic 80; weight, 151 lbs.

The patient was a well-nourished colored man in no distress. The pupils reacted

actively. The teeth were in bad condition. There were no enlarged lymph nodes. The thyroid was not enlarged. The lungs were clear except for a few râles at the bases. The heart was enlarged especially to the left. At the apex there was a blowing systolic murmur transmitted to the axillary area. In the aortic area there was a harsh, rough systolic murmur transmitted into the vessels of the neck. There was a systolic thrill felt over the base. There was a blowing diastolic murmur down the left border of the sternum. There was marked peripheral pulsation and the pulse had a decided collapsing quality. The peripheral vessels were tortuous and thickened. The abdomen was somewhat distended and there was thought to be free fluid in the peritoneal cavity. The edge of the liver was felt three fingers-breadth below the costal margin. The spleen was not felt. The reflexes were all normally active.

The specific gravity of the urine was 1.024. There was a trace of sugar, no albumin. The Wassermann reaction on the blood serum was negative.

Roentgenogram: Fluoroscopic Examination: Heart enlarged; aorta diffusely dilated and rotated; no evidence of aneurysm. Some increase in the peribronchial markings. Marked infiltration at the bases probably secondary to the cardiac condition.

Film: Cardiac shadow enlarged; aorta dilated. Secondary changes in both lungs.

The patient returned to the Out-Patient Department September 4, 1936. On that occasion the Wassermann reaction was found to be positive. He then was quite short of breath and there was edema of the legs. A roentgenogram is reported: Cardiac shadow enlarged; aorta dilated; secondary changes in both lungs. Interlobar thickened pleura, right side.

The patient was admitted to the hospital September 22, 1936. There he stated that following his visit to the Out-Patient Department in December 1933 he had been quite comfortable until six weeks before this admission. Then shortness of breath on exertion had developed and gradually had increased so that he had been unable to lie down in bed and had had to spend the nights sitting in a chair. His ankles had been swollen for a month.

Examination. Temperature, 99.5°; pulse, 96; respirations, 28; blood pressure, systolic 115, diastolic 50.

The patient was described as a short, squat, pudgy-looking, middle-aged Negro. He was propped up in bed with only moderate respiratory distress. The veins in the neck were engorged. The pupils were equal and active. There were no enlarged lymph nodes. The thyroid was not enlarged. There were coarse râles at the bases of both lungs. On the right below the angle of the scapula the percussion note was a little impaired and the breath sounds were somewhat diminished in intensity. There was violent pulsation over the heart. The apex beat was a forcible thrust in the seventh interspace at the anterior axillary line. At the apex both a systolic and a diastolic murmur were heard, the latter becoming louder toward the base. The diastolic murmur was particularly loud to the left of the sternum. No thrill could be felt. The right pulse was somewhat fuller than the left. The blood pressure was the same on both sides. The abdomen was somewhat distended. The edge of the liver was felt three fingers-breadth below the costal margin. The genitalia showed no abnormality. The rectal examination was negative. The reflexes were obtained but were somewhat hypoactive.

Course in the Hospital. On admission the temperature was somewhat elevated and during the following four days it varied between 101° and 103°; then for three days it fell almost to normal but soon rose again varying at first between 99° and 102°, later between 101° and 104°. There was a moderate degree of anemia. From time to time there were severe attacks of dyspnea. At other times he was delirious. A friction rub developed over the right lower lobe and the roentgenogram showed evi-

dence of consolidation, it is stated in the report, of the right upper lobe. Later there were dullness and fine râles over the upper portion of the left chest and a roentgenogram showed spreading consolidation on the left side. There was very little cough and almost no expectoration. Still later, signs suggesting fluid in the right pleural cavity developed. On October 10 the right pleural cavity was tapped and 30 c.c. of bloody fluid were removed, which contained 12,500 leukocytes per cu. mm. Most of

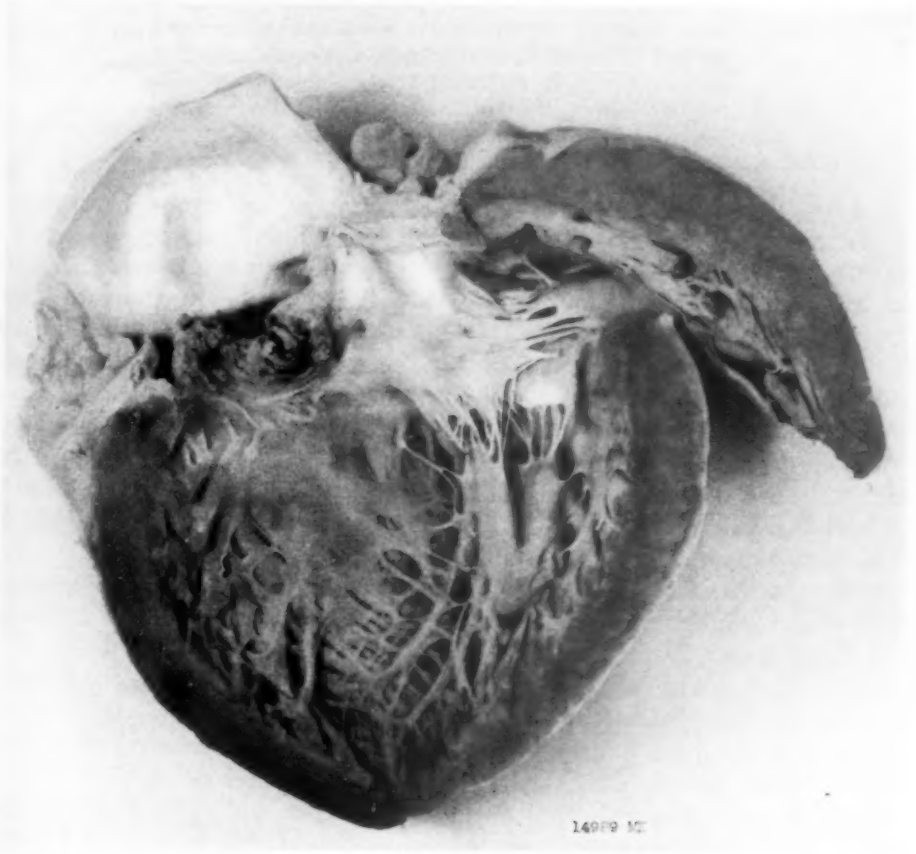

FIG. 2. Heart of Case 2. For description see text.

the cells were polymorphonuclears containing gram-positive diplococci. There were also chains of diplococci, thought to be pneumococci, in the fluid. Cultures yielded a heavy growth of Alpha streptococci. As these signs in the lungs were developing the temperature and pulse rate rose to a higher level, the patient became more and more irrational and exhausted, and while desperately ill he died suddenly on October 10, 1933.

Laboratory Examinations.

Blood Count: Hgb. 58 per cent; R.B.C. 4,570,000; W.B.C. 6,920.
Later the leukocyte count rose and varied from about 10,000 to 20,000.

Blood Culture: No growth.

Urine: Specific gravity 1.023. No sugar. A large amount of albumin on admission, later none. Many leukocytes and a few casts in the sediment.

Roentgenograms:

9/26/36. Chest: General haziness of lung field probably due to movement of patient. Area of consolidation of right upper lobe, probably lobar pneumonia.

10/2/36. Chest: There is now clouding in the left mid-lung field compatible with pneumonia.

10/8/36. Chest: Heart and aorta apparently enlarged. Diffuse clouding in right lung especially in mid-portion, probably pneumonia.

10/9/36. Chest: There is only a small amount of fluid in the right chest; the majority of the changes are due to a pneumonic process.

Electrocardiogram: Fairly deep S-waves in Leads I and II. T_1 upright and small. Low take-off of S–T segment in Lead II, ending in a biphasic T-wave. T_3 inverted. Changes in Leads I and II compatible with those seen following pulmonary embolus. T-wave changes probably are due to digitalis.

From these clinical data I do not see how it would be possible to make any diagnosis of the heart condition other than syphilitic aortitis with aortic insufficiency. The patient had been examined three years before the onset of his final illness and at that time showed the characteristic signs of aortic insufficiency. He had had mild symptoms of myocardial failure but no fever, no embolic phenomena and no splenic enlargement. The Wassermann reaction had been positive. Then followed a period of nearly three years without symptoms, at the end of which shortness of breath and swelling of the ankles again came on. During his second admission to the hospital the illness was dominated by the symptoms of a severe pulmonary infection which was correctly diagnosed as an infected pulmonary infarct. The symptoms of myocardial failure were inconspicuous.

Autopsy revealed the characteristic lesions of bacterial endocarditis which had almost completely healed. In stained sections the infecting organism was a gram-positive coccus, in all probability the *Streptococcus viridans*. There was no evidence whatsoever of a past or present rheumatic infection or of syphilitic aortitis. It may be that the aortic valves were congenitally bicuspid but, on account of the great deformity of the valves caused by the infection, this point could not be definitely settled.

When we consider the clinical course of events, and view the conditions found at autopsy, we cannot resist the conviction that in this patient the bacterial endocarditis eventually would have healed, had he not died untimely of the pulmonary complication.

Portions of the autopsy report are added.

Anatomical Diagnosis: Subacute bacterial endocarditis aortic valve; dilatation and scarring of sinuses of Valsalva (healed mycotic aneurysms; malformation?; ulceration); scarring of mitral valve; hypertrophy and dilatation left ventricle; scars, left ventricle; mural thrombi auricular appendage; emboli in pulmonary arteries; infarcts; infected gangrenous infarct, right lower lobe; infarcts in spleen; hemorrhages in kidneys; hemorrhagic pleural effusion, right; ascites; chronic passive congestion lungs and liver; small angioma of liver.

Dr. W. C. MacCallum's note on the heart: The heart is quite large; the surface in general is smooth but there are pearly patches over the right ventricle and small

lenticular nodules along the coronary arteries. The coronaries are fairly straight. The left anterior descending branch shows some patches of sclerosis; these are very thin. The right is almost smooth throughout. The right auricle shows a smooth endocardium. There is a very small thrombosis in the tip of the auricular appendage. The tricuspid valve is in part quite delicate. A portion of it shows a thickening and rolling of the margin and shortening of the chordae tendineae.

The pulmonary valves are delicate. The left auricle seems hardly changed. The mitral valve is a little thickened along its line of closure and perhaps slightly contracted. The aortic leaflet of the mitral valve shows a curious translucency throughout most of its extent with a margin of more opaque white. There it is roughened a little by dark red flecks which are extremely small. There is no actual vegetation to be seen. At the beginning of the posterior leaflet there is very marked thickening which has been taken for section. This has a roughened and reddened surface and on section is about 4 mm. thick, translucent and gray. It passes on into the chordae. Along the aortic segment particularly the chordae tendineae are thickened and apparently fused along the thickened margin of that valve. Along the edge of the other valve, that is the posterior segment, they are separated but there is a distinct thickening extending at least to the middle of the valve, of the margin and the line of closure.

The margin of the sinus of Valsalva at the root of the aorta is so completely altered that only a photograph or sketch can describe it. The aortic valves are practically fused together. There is only one point at which the ordinary approach of two valves to one another is seen and that is at the base of the mitral between half of the left segment and half of the posterior segment. The rest forms one thick, rigid band which is perforated by a large hole and by smaller holes, white and roughened and covered with vegetations but the sinuses are all run together as far as they lie behind this great shelf-like structure.

The orifice of the left coronary is wide; that of the right coronary is very wide but seems practically unchanged, although in the remaining space which extends deep down below these coronary orifices, there are great depressions lined by pearly scar-like material, in places covered by fresh vegetations, in places extending so as to isolate cord-like strands from the aorta down to the sinus.

Just above the level of the sinus of Valsalva the aorta becomes perfectly normal and smooth. This, however, extends only to about the middle of the arch. Below the aortic valve the septum membranaceum is thickened by gray or pearly bands. The back of the mitral valve is rigid, yellowish and roughened. Toward the aortic valve it is much more roughened, evidently from the implantation of a vegetation. The myocardium is not much affected.

The aorta past the margin of the large vessels shows some sclerotic change. Below that in the thoracic aorta the wall is fairly elastic. It is flecked with tiny patches of whitish opacity and there is a delicate striation along the whole course. These flecks become a little more emphasized below the renals and there are some yellow patches.

The left lung is smooth externally throughout the upper lobe. In the lower lobe there are two projecting patches which are somewhat reddened. On section the upper lobe seems air-containing except for a small patch which is fairly firm in the lower part. In the middle of the lower lobe there is a quite distinct infarct.

The right lung shows a fibrous, somewhat hemorrhagic exudate on the surface. The upper lobe shows a patch of consolidation in its lower margin which on section is somewhat hemorrhagic and shows a thrombus in the central blood vessels. It is quite sharply outlined. It has in general the appearance of an infarct. In the middle lobe the brown pigmentation of the lung is particularly striking but it seems to be air-containing throughout.

In the lower lobe there is a large area of consolidation which is deep red and has

in general something of the appearance of an infarct but the central part is hollowed out into ragged cavities with greenish, discolored walls which communicate with one another. The large vessel passing to this area is plugged by a thrombus.

Microscopical notes: Cultures from the valves showed many different organisms. In smears the predominant organism was a gram-positive coccus occurring in threads and in long and short chains.

CASE III

W. S., 50 years, male, colored, single.

A colored laborer, 50 years of age, entered the Johns Hopkins Hospital, January 24, 1934, complaining of shortness of breath. He had been in the hospital previously from January 16 to January 19, 1922. The diagnosis was syphilis, aortic insufficiency, chronic alcoholism. Following his discharge in January 1922, the patient

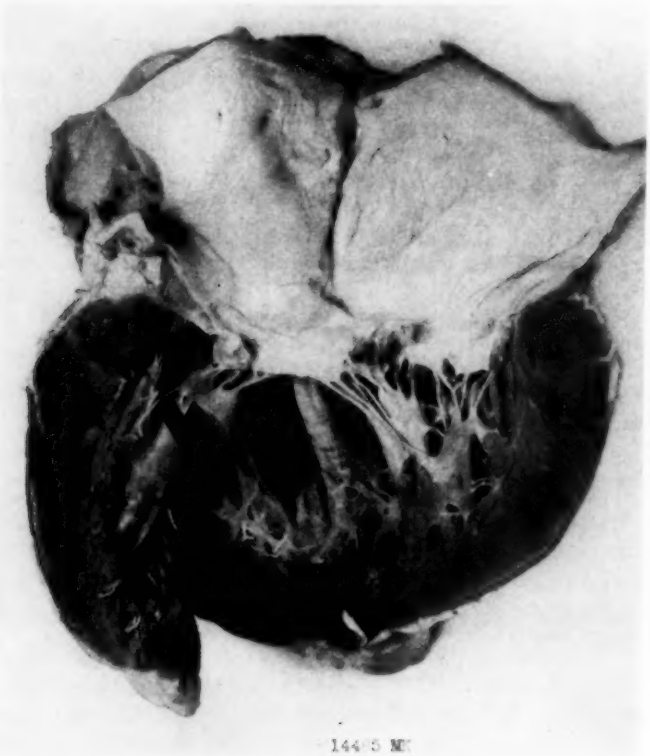

FIG. 3. Heart of Case 4. For description see text.

apparently had gotten along well and had worked hard. When admitted to the hospital January 24, 1934, he said he had been somewhat short of breath for a great many years but this had caused him no great inconvenience until December 1933 when he had become progressively more and more short of breath and the ankles and legs had become swollen. At the end of December he had had some fever and from then on his shortness of breath had become very severe. He had been unable to lie flat in bed; indeed, had spent most of the time sitting in a chair.

Examination. Temperature, 99.6°; pulse, 100, respirations, 26; blood pressure, systolic 190, diastolic 60.

The patient was in great respiratory distress; it was difficult for him to talk on account of the shortness of breath; his respirations were rapid and labored. He had an anxious expression. He had a rasping cough and occasionally brought up a little mucoid sputum. Breathing was Cheyne-Stokes in character. There was marked edema of the legs and over the lower part of the back. He was very cyanotic. The eyes were normally prominent, pupils equal, regular, reacted actively to light and on accommodation. Extra-ocular movements were well performed. The retinal arteries were somewhat narrow and tortuous, and the veins rather full. The teeth were in very poor condition. The pharynx was somewhat injected. No enlarged superficial lymph nodes. Thyroid not enlarged. The chest was full and rounded, symmetrical. The lungs were clear except for numerous moist râles over the lower lobes. The heart seemed to be greatly enlarged. No localized apex beat could be made out. The area of cardiac dullness measured 4 cm. to the right and 12 cm. to the left of the midline. There was a band of dullness over the manubrium measuring 7 cm. The heart's action was very rapid but regular. At the apex a definite thrill could be felt; its time in the cardiac cycle could not be determined. The first sound at the apex was very loud and was preceded by a rumbling murmur, late in diastole; it was accompanied and followed by a soft, blowing systolic murmur. Over the body of the heart there was a proto-diastolic gallop. In the aortic area the sounds were heard with difficulty. There was a distant, rough systolic murmur; the second aortic sound was not clearly distinguished and seemed to be replaced by a diastolic murmur which was heard also to the left of the sternum. The second pulmonary sound was accentuated. The pulse was regular, moderately collapsing in quality; a capillary pulse was visible in the nails. There was moderate thickening of the peripheral vessels and considerable throbbing. The abdomen was prominent, there was a moderate degree of ascites. The liver was enlarged, extending a hands-breadth below the costal margin. The spleen was not felt. Genitalia showed nothing abnormal. The reflexes were normally active.

Course in the Hospital. The patient made a prompt and remarkable recovery. After three or four days he was comfortable and at the end of five days was able to lie flat in bed. As the heart rate slowed the sounds could be more carefully observed. The apex beat now could be felt in the sixth interspace almost as far out as the anterior axillary line. All observers agreed that the first sound at the apex was loud and that there was a definite rumbling murmur late in diastole. There also was a systolic murmur and an early diastolic murmur. At times the diastolic murmur at the base was not very pronounced and some observers even doubted the existence of aortic insufficiency. However, in the end everyone agreed to the presence of aortic insufficiency and most observers were of the opinion that there was definite evidence of mitral disease as well. There seems to have been a remarkable reduction in the size of the heart as the patient improved, for a roentgenogram taken shortly before his discharge shows the heart to be but little enlarged. As the patient improved a very loud systolic murmur was heard in the tricuspid area. The blood pressure on admission was elevated, on one occasion as high as systolic 200, diastolic 90. As he improved the blood pressure gradually fell and when he was discharged from the hospital the reading was systolic 142, diastolic 58. On one occasion it had been as low as systolic 112, diastolic 56. He was discharged in good condition on February 27, 1934.

Laboratory Examinations.

Blood Count:	Hgb.	R.B.C.	W.B.C.
On admission	74 per cent	3,700,000	12,750
On discharge	110 per cent		7,840

Wassermann reaction on the blood serum: Negative.

Blood Culture: No growth.

Urine: Specific gravity 1.016 to 1.022. A trace of albumin. No sugar. A moderate number of leukocytes and a small number of casts in the sediment.

Temperature on admission varied from 98° to 100°. On discharge it was oscillating between 98.6° and 99.6°.

Electrocardiogram: Normal sinus rhythm. Levogram. Slight slurring of QRS complexes in all leads. T-waves inverted in I and II, iso-electric in Lead III.

Roentgenogram:

Chest: Cardiac shadow slightly enlarged. Tuberculous, fibroid infiltration left upper and middle portion of lung.

Tele.: M.R. 4.7; M.L. 9.8; A. 6.2; T. 28

After discharge from the hospital on February 27, 1934, the patient made a number of visits to the Out-Patient Department and then returned no more. On October 22, 1936, he was admitted to the City Hospital desperately ill and died later on the same day. He stated that during the two previous months he had suffered from ever increasing shortness of breath, swelling of the legs, and cough with frothy, blood-tinged sputum. Only a hurried physical examination could be made, the notes of which record moderate enlargement of the heart, the signs of mitral stenosis and insufficiency, and the usual evidence of chronic passive congestion. The signs of aortic insufficiency were overlooked or misinterpreted.

Considering the clinical evidence presented by this patient one is forced to make the diagnosis of rheumatic heart disease. He was first observed in 1922 at which time he had a characteristic aortic insufficiency without symptoms. He remained well until 1933 when the first symptoms of myocardial failure came on. Again, examination revealed the signs of aortic insufficiency and in addition the signs of a mitral lesion. He died of heart failure in 1936, fourteen years after the valve lesion had first been discovered.

I shall not dwell upon the erroneous diagnosis of mitral stenosis, for it is only too well known how difficult it is to decide upon the condition of the mitral valves in the presence of aortic insufficiency. I wish merely to remark that the clinical assumption that in addition to aortic insufficiency the patient did have mitral stenosis, made the diagnosis of rheumatic heart disease seem doubly secure.

As a perusal of the autopsy notes will show there was no disease of the mitral valves. Only the aortic valves were affected and these in a manner which leaves little doubt that the original infection was bacterial and not rheumatic. We must realize that it is never possible from the inspection of old healed scars to state with complete assurance the precise nature of the injury which caused them. However, in this instance the appearance of the valves is so characteristic that a positive statement is justified even though not entirely certain.

Anatomical Diagnosis: Scarring, calcification, insufficiency and stenosis of the aortic valve (healed bacterial endocarditis?); calcified plaques above commissures of the aortic valve; history of treated syphilis; history of hypertension; cardiac hypertrophy and dilatation; scars in the myocardium and epicardium; chronic passive congestion; anasarca; calcified tubercle at apex of left lung and in left bronchial lymph node; slight emphysema and anthracosis; (long standing history of mitral stenosis).

Dr. S. S. Blackman's note on the heart: The heart is quite large. The chambers are all dilated and hypertrophied but the hypertrophy is chiefly on the left side. There are a few tendinous patches on the epicardial surface. The tricuspid valve is practically normal. At one point, there is slight thickening along the line of closure of one anterior leaf. The left auricle shows no evidence of an old rheumatic patch. The mitral valve is practically delicate and looks anatomically competent. At the junction of the anterior and posterior cusps, there is a slight thickening along the line of closure in a small localized area. The endocardium above is very finely granular. The chordae tendineae are not scarred or shortened. There are only a few small yellow patches in the aortic leaf of the mitral valve. The aortic cusps are all very much thickened and deformed. The thickening and calcification which are marked are most marked along the line of closure and the changes further down where the valves fuse with the endocardium of the septum are much less marked. The commissures are all greatly thickened and not calcified. There are calcified nodules projecting toward the ventricle and into the sinuses of Valsalva. There is a good-sized, circumscribed plaque in the aorta at the point of insertion of each cusp. These plaques are now calcified. The largest one is above the point of insertion of the right and left cusps and this plaque is about 2 cm. in diameter. The adjacent margins of the right and left aortic cusps below this plaque are fused together to form a calcified mass which is nearly 1 cm. wide. It bulges out towards the ventricle for nearly an equal distance and where the separation finally does take place, there is a wide gap between the two in which there is a little coagulated blood and some yellowish granular material suggesting fibrin. All of the altered commissures are pulled down and somewhat retracted and the valve is evidently insufficient and somewhat stenosed too. The mouths of the coronaries are not narrowed and there is very little coronary sclerosis. However, one can see definite gray scars in the myocardium near the base. In the posterior papillary muscle there are numerous evident gray scars. There is not enough evident sclerosis of the coronary arteries to account for these scars. However, the mouth of the right coronary lies between the two plaques already described, and these do extend in the aorta as far as the very edge of the coronary mouth. Although it is not narrowed, the elasticity of the aorta on either side of it is evidently lost. The ascending aorta besides the plaques mentioned is perfectly delicate and smooth for in the rest of the aorta too, there is very little sclerosis. There are a few calcified plaques in the arch and in the lower part a few yellow streaks and one or two little calcified plaques but no definite syphilitic lesions and really very little arteriosclerosis.

The other organs show chronic passive congestion.

Case IV

G. D., 65 years, female, white, divorced.

A white woman, 65 years of age, entered the Johns Hopkins Hospital October 12, 1935, complaining of shortness of breath and swelling of the legs. She always had been a hard-working woman and was well until four years before admission when she began to have attacks of indigestion. The symptoms became so severe that she entered a hospital at Philadelphia where they treated her by washing out the kidneys. After leaving the hospital she began to notice shortness of breath on exertion and occasionally the ankles were somewhat swollen. The shortness of breath gradually increased and at the end of 1933 she was so troubled with dyspnea and swelling of the legs that she had to give up her work and go to live with a relative. Even though she now lived very quietly she did not improve. Her shortness of breath finally became so severe that she entered a hospital at Lebanon, Pa. When she left the hospital at the end of five weeks she was much better.

One year before her admission she had an upper respiratory infection and all

of her old symptoms returned. She was quite short of breath and her legs were swollen. From then on she was always short of breath and the ankles were swollen from time to time. Five weeks before entering the hospital the abdomen began to swell and her shortness of breath became more and more severe. Three days before admission she had nausea and severe vomiting. She came to Baltimore and was admitted to the hospital through the Accident Room.

Examination. Temperature, 98.4°; pulse, 145; respirations, 28; blood pressure, systolic 166, diastolic 110.

The patient was a well-developed, well-nourished woman propped up in bed with a moderate degree of respiratory distress. She was very deaf which made it difficult to get a detailed history. There was a little cyanosis of the lips and nails. There was extensive edema of the legs, ankles, thighs, over the sacrum and back and a little over the arms and wrists. The eyes were normally prominent, pupils were equal, reacted actively. There was a slight arcus senilis. The retinal veins were somewhat engorged; the arteries somewhat narrowed and tortuous though not conspicuously so. There was slight compression of the veins where the arteries passed over them. A few small recent hemorrhages were seen. All the teeth had been extracted. The pharynx showed nothing remarkable. There was no enlargement of the superficial lymph nodes. Thyroid was not enlarged. The chest was well formed; it moved somewhat as a whole. The lungs were clear except for a few moist râles over the lower front on both sides and in back below the angle of the scapula. The apex beat of the heart was in the fifth interspace 9 cm. to the left of the midline. Area of cardiac dullness measured 5 cm. to the right and 11½ cm. to the left of the midline. The heart's rhythm was totally irregular. The first sound at the apex was followed by a very loud, blowing systolic murmur. At the base the second pulmonary sound seemed to be louder than the second aortic. The peripheral vessels were tortuous and thickened. The pulse was equal at the two wrists, totally irregular. The abdomen was greatly distended. There was evidence of considerable accumulation of ascitic fluid. The edge of the liver was felt 9 cm. below the costal margin. The spleen was not felt. The neurological examination was negative.

Course in the Hospital. The patient was twice bled and given digitalis but there was little if any improvement in her symptoms. Later a profuse diuresis occurred after which the edema lessened, the dyspnea was less oppressive and the patient became more comfortable. However, this improvement lasted but a short while; soon she was just as much swollen as before, her breathing was difficult and she became quite drowsy following the liberal administration of ammonium chloride. On October 27 she began to vomit, she rapidly grew worse and died later that day.

Laboratory Examinations.

Blood Count: Hgb. 115 per cent; R.B.C. 5,040,000; W.B.C. 10,000.

Wassermann reaction on the blood serum was strongly positive.

Blood chemical studies:

	NPN	CO_2	Plasma Prot.
October 12	34 mg. per cent		
October 18	34 mg. per cent	56	6.8 gm.
October 21	60 mg. per cent		6.5 gm.
October 24		27.7	

Spinal Puncture: Colorless fluid. 2 cells. Negative Pandy. Negative Wassermann reaction.

Urine: Specific gravity 1.009 to 1.020. No sugar; albumin—a trace. A small number of leukocytes and an occasional cast in the sediment.

The temperature varied from 96° to 100°.

The pulse rate varied from 80 to 140.

Electrocardiograms:

October 18, 1935: The dominant rhythm is nodal. There are extrasystoles occurring at every second beat giving rise to a typical bigeminal rhythm. There are occasional paroxysms of extrasystoles arising from a different ectopic focus giving rise to runs of paroxysmal ventricular tachycardia at a rate of 125.

October *27*, 1935: Auriculo-ventricular nodal rhythm. Dextrogram. Nodal tachycardia.

Here we have a characteristic instance of mitral stenosis in a woman 65 years of age, the symptoms first appearing late in life. Under these circumstances we are seldom wrong in concluding that the lesion is the result of a former rheumatic infection. However, in this instance the scarred appearance of the valves as seen at the postmortem examination resembles much more closely the results of a bacterial than of a rheumatic infection. I do not pretend that the distinction can be made with confidence although I think the evidence makes the conclusion highly probable.

Anatomical Diagnosis: Mitral stenosis and calcification. Cardiac hypertrophy. Chronic passive congestion of viscera. Syphilis (Wassermann). Arteriosclerosis. Localized atrophy of kidney from arterial sclerosis. Hemorrhages in urinary bladder.

Dr. S. Jarcho's note on the heart: The heart which weighs 550 gm. is distinctly larger than normal. There is perceptible dilatation of the right auricle. The tricuspid valve presents a moderate degree of fibrous thickening along the line of closure especially marked on the anterior leaflets. The chordae tendineae are opaque but not appreciably shortened. There is distinct hypertrophy of the right ventricle. No changes are found in the pulmonary cusps. The left auricle is markedly dilated and moderately hypertrophied. The endocardium is thickened but no discrete auricular patch is seen. The mitral orifice is much narrower than normal and is fixed by the calcification of part of the valve. When the valve is opened its edge is seen to have formed a thickened shelf with rounded edge; irregular, rough calcified masses are found at intervals along the valve. The chordae tendineae are greatly shortened. They are opaque and end without ramifying. The endocardium over the apices of the papillaris muscles is distinctly opaque and the papillaris muscles themselves are much broader and thicker than normal. There is distinct eccentric hypertrophy of the left ventricle. The aortic cusps are very little thicker than normal but are fused for approximately 4 mm. along the respective commissures. The corpora arantii are not altered. No verrucae are seen. The myocardium is somewhat flabby and contains a very few inconspicuous scars.

Microscopical Notes: Section through the left ventricle, left auricle and mitral valve shows thickening and fibrosis of the valve and of its base with no signs of active inflammation. The auricle is thickened in the endocardium and myocardium. The latter shows mononuclear infiltration but not characteristic of Aschoff bodies. Similar infiltrations are encountered in the epicardium which in addition is slightly scarred. The ventricular myocardium shows a few perivascular scars and one vascular collection of round cells.

Additional section shows dense hyaline thickening of the mitral valve and a small area of calcification. The myocardium presents scattered tiny mononuclear infiltrations which are not numerous and not regularly perivascular. The coronary vessels show very slight intimal thickening.

Other sections taken through the anterior papillaris muscle, left ventricular and auricular ring, the intraventricular septum and right ventricle and pulmonary valve show a few tiny myocardial scars. There is no evidence of active inflammation.

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AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR OF DOCTOR JOSEPH HERSEY PRATT

THE PSYCHO-BIOLOGY OF BREATHING*

By CARL BINGER, M.D., *New York, N. Y.*

THIS paper deals with what I have called the psycho-biology of breathing and its relation to diseases of the respiratory system. In it I have attempted to review the essential physiological facts of respiration and to indicate, when possible, links between our physiological and psychological knowledge. The connections will not always be obvious, but it seems a sound method of procedure to begin with known facts in each field and to try to bring them into relation with each other.

It may be objected by some that the laws of the body do not govern the laws of the mind—that the chasm which separates these two hemispheres cannot be bridged and certainly not by arguments based on analogy. I suspect that the split exists partially within us—is part of our own subjective ambivalence which we project on to the material under investigation and that even such divergent technics of inquiry as physiology and psychoanalysis are not so remote from one another as certain purely fortuitous circumstances have made them appear to be.

The method of psychoanalysis has contributed much to our understanding of neurotic disorders. It has provided us also with an entering wedge into some of the more obscure etiological problems of so-called functional and organic disease. But no one will deny that our knowledge is still in the form of first and rough approximation. We must try, as Santyana used to say "to define the limits of our ignorance." Nor need there be any quarrels between so-called organicist and functionalist—if that is the proper title to give his adversary. No one has a sole proprietary right to explore the secrets of nature; and each man must select the method of study that is congenial to him.

Let me now proceed to more practical matters:

A young European girl of aristocratic origin and background made up her mind against her parents' will to go to a university. She had always been a somewhat shy, reticent, easily depressed child readily inclined to tears, and rather solitary. There were many difficulties at home. The parents were not happily married. There was much friction in the atmosphere and little love, although her mother was constantly concerned with the daughter's welfare. The girl had outspoken artistic interests. She loved music, the theatre and had a respectable talent for drawing. She was on the other hand greatly interested in languages—wavering indeed between the two interests. This was a source of conflict not only in her but between her parents and herself. Finally she decided to pursue the study of languages and only after much persuasion and against great resistance could she win her parents' unwilling consent. They were by no means liberal with her in financial matters so that at the university she lived

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in modest isolation. In the course of the second semester she began to realize that academic work was not giving her the release and satisfaction she had hoped for. Naturally this made her very unhappy but she tried with all her might to push through her plan to study, if only not to be upbraided by her father. She dragged along until the close of the semester hardly able to follow the lectures properly.

During the holidays she returned home only to hear reproaches because she looked so badly and because of her moods. She was sent to a doctor who found nothing. Constantly she was assailed by doubts as to the wisdom of further pursuing her studies. After a most unpleasant scene with her parents she became depressed and then began to cough. This again took her to the doctor who could find nothing. But the cough persisted. Upon returning to the university she consulted a specialist who at first found, as we say, nothing in her chest, but repeated examinations and roentgen-ray studies disclosed an incipient process at the right apex.

The second case I wish to describe concerns a man in his early thirties, always in excellent health, in good financial circumstances and happily married to a young woman also apparently in perfect health. During her untroubled pregnancy the husband pursued his usual business activities, was much engaged in sports, indeed even rode in steeple-chases. The wife's delivery was difficult and shortly thereafter she began to fail from what was subsequently proved to be a hydatid mole. Her illness lasted about a year when she died. The husband had not given up hope of recovery until a few weeks before the end, and in spite of his intense worry he continued in good health. As soon as the hopelessness of her condition became clear to him he began to feel badly, became depressed and quite lost his joy of living. After his wife's death his depression grew worse. Within a few weeks he had a slight pulmonary hemorrhage which he himself did not relate to a disease of the lungs, as such a possibility had not occurred to him. Upon examination, however, the diagnosis of phthisis was established.

These two abstracts of case histories are taken from a book by E. Stern[1] called " Die Psyche des Lungenkranken " which discusses wisely and sympathetically such problems as the reaction of patients to a diagnosis of pulmonary tuberculosis and to sanatorium life, the relationship of doctor and patient in chronic illnesses, the psychic factors in the etiology of tuberculosis. He includes a series of skillful vignettes of patients' lives in which are described, as in the ones which I have reported, long periods of tension, ambivalence and frustration which lead gradually to fatigue states, hopelessness and depression and in which the denouement is the discovery of an apical process, with a temporary resolution of the conflict by sanatorium treatment.

An extensive literature has sprung up in this field. Within the past five years the Quarterly Cumulative Index has published a new subheading: " Mental Aspects " under Tuberculosis. Naturally we do not know what mechanisms are involved here—nor how states of tension and conflict prepare the body for the invasion of the tubercle as they appear to do. It is of importance in the first instance to establish the fact of such relationships before essaying the far more complex problem of explaining them. This first step then is a practical point of departure—a more complete and psychiatric, if you will, anamnesis of patients suffering from incipient pulmonary tuberculosis.

What we observe in these life histories is a coincidence of events. Per-

haps it would help us if we dismissed from our minds, for the moment thoughts of causality, clichés about psychogenic and somatic disease or functional versus organic and looked upon these examples and upon others, which I will present as simultaneous physical and mental phenomena. From a metaphysical point of view as well as from that of modern physics the question has been raised as to whether the discussion concerning cause and effect about which we talk with so much assurance and dogmatism has in it any inherent logic other than one of temporal and statistical relationship. And so I should like to stress as our point of departure the idea of *coincidence:* the coincidental happenings in the realm of the mind and of the body in relation to certain specific inner trends and outer situations. This mode of orientation toward our patients is important as it will affect our clinical judgment both in diagnosis and treatment.

I have dealt here with pulmonary tuberculosis first because it represents one of the most important of the diseases of the respiratory apparatus, secondly because problems of pulmonary ventilation may have an etiological bearing on the location of the lesion. If psychological determinants play a part in the occurrence of this disease it is reasonable to shift our ground for the moment and to look upon the phenomenon of pulmonary ventilation from this point of view as well. Speaking teleologically breathing is designed to supply the tissues with oxygen. This function is so vital to survival of the organism that we may expect to find that forces voluntary and involuntary, reflex chemical, homeostatic as well as affective, combine to insure its perfect performance.

Breathing is in more than one sense a twofold function. It is usually thought of as consisting of an external and internal process. External respiration has to do with bringing the organism into gaseous equilibrium with its outer atmospheric environment. Internal respiration is concerned with the transport of gases in the blood stream and their diffusion to the tissue cells. The exchange of gases takes place at the surface of the respiratory epithelium whither the air properly warmed and moistened has been brought after its passage through the upper respiratory tract. Here we see a rough analogy to the preparation of food in the mouth before it passes down the gullet into the stomach. I shall refer again to this analogy.

Breathing is normally adjusted to maintain a fairly constant composition of the alveolar air, because the alveolar air regulates the tension of gases in the arterial blood. Enough fresh air has to be introduced into the alveoli to replace the oxygen taken up by the blood, and to get rid of the CO_2 which has come out of the blood. The venous blood which comes to the lungs gives off CO_2 and takes up oxygen until it comes into equilibrium with the air in the alveoli. The tension of gases in the arterial blood is therefore normally about the same as in alveolar air. As we shall see later this reciprocally related process of oxygen absorption and CO_2 elimination not only insures adequate ventilation of the blood and tissues but also affects

the function of the respiratory center which is extraordinarily sensitive to changes in tension of gases in the blood.

Embryologically the pulmonary respiratory apparatus develops from the hind part of the ventral wall of the head gut. Immediately behind the thyroid gland a median groove, the rudiment of the trachea, is detached from the gullet. From its hinder end a couple of vesicles develop—the simple tubular rudiments of the right and left lungs. As the respiratory apparatus is genetically and structurally related to the gastrointestinal tract, so its function seems to present an analogue of the latter. I do not mean to imply that the analogy of function derives from their common site of origin though this is an interesting field for speculation. However, both systems are concerned with the incorporation of certain substances of the external environment, with the transport of these substances to the tissue cells and with the excretion of certain products of tissue metabolism. Both digestive and respiratory systems seem susceptible to similar derangements, for example: to spasms, to forced expulsion, to changes in secretion and both may become pathways for the entrance of infectious organisms. If Alexander[2] is correct in his assumption that the gastrointestinal tract may act out certain emotional trends having to do with ingestion, retention and elimination it is conceivable that an organ system presenting aspects so closely parallel embryologically and functionally to it can exhibit similar responses for embodying similar trends. It remains, however, for future scientific inquiry to explore the problem of psychological engrams as it has undertaken to do with physiological ones.

We have just seen that the respiratory apparatus in its rudimentary embryological form consists of a system of simple tubes. From the phylogenetic point of view this same fact holds. In the lower forms, as for example the insectivora, there are no lungs but tracheae through which atmospheric oxygen passes by simple diffusion. It is believed that respiratory movements begin at that point in the phylogenetic scale where the size of the organism and the length of its tracheae no longer permit adequate ventilation at the existing partial pressure of atmospheric oxygen. An interesting parallel to this concept can be observed in man, whose respiratory movements may disappear when he is placed in an artificial environment in which atmospheric pressure is caused to fluctuate rhythmically above and below normal pressure. Again we are confronted by an analogy with the gastrointestinal system. The fetus is nourished passively by diffusion and osmosis through the chorionic villi—only later after birth to use actively its sucking and swallowing mechanism for the ingestion of food. From a phylogenetic point of view we see in the lower forms, such as protozoa, nourishment occurring by osmosis and diffusion and only much later the differentiation of gastrointestinal tracts and the establishment of mouth parts equipped for sucking, biting, chewing and swallowing.

In the field of psycho-pathology we are familiar enough with patients

who refuse to eat even to the point of starving themselves to death. Similar reactions to breathing are not so common but are by no means unheard of. One needs to think only of the stubborn angry child who holds his breath in a temper tantrum to the point of cyanosis, of the Sudanese negro who can die of asphyxia by holding his breath, and of the common and ancient form of suicide by strangulation or hanging, which like other forms of suicide is thought to express certain unconscious determinants.

As there is an analogy in the structure and function and in what might be called the psycho-pathological equivalents of these two systems so also are there certain linguistic forms the use of which suggests parallel origins. I shall mention only the fact that deep labored breathing of diabetic coma and acidosis is sometimes described as "air hunger." Many individuals during periods of tension or excitement actually swallow air.

Psychoanalysts are familiar enough with these substitutions of one organ system for another and of what appears to be—perhaps because of our lack of understanding—the welter and confusion of unconscious thought. The breath, for example, may take on the meaning of food and both may be related to fantasies of impregnation. Words may be feces: the voice the phallus. Bizarre as these interpretations may sound they are in fact not interpretations but what our patients often tell us if we are willing and able to listen to them.

Continuing with the theme of organ displacement we are familiar with vasomotor changes such as blushing and the engorgement of the erectile tissue of the nasal turbinates, which are related to emotional disturbances; also with so-called vicarious menstruation and with the treatment of dysmenorrhea by applications to the nasal mucous membrane. Whether this therapeutic procedure is founded in fact or fantasy I do not know. Frequently we encounter the so-called hysterical globus phenomenon which appears also to be a displacement and often to be related to fantasies of oral impregnation. I had recently the opportunity to observe one in *statu nascendi* and since the respiratory system was at least subjectively involved I shall describe it.

A woman of 25, married but childless, who is suffering from a severe mixed neurosis in which anxiety states and obsessional ideas predominate, was recounting a nightmare to me. She could not recall its content—only the fact that she felt an enormous weight on her chest and that she was unable to get her breath or utter a sound. This is a familiar enough setting for nocturnal terror. While she was talking the feeling returned. She lay quite motionless and said that she felt a great weight pressing on her chest as if she were unable to breathe. She then said: "Aren't there stories about cats lying on babies' chests and sucking their breath away." This patient was brought up in intimate association with a pet cat who in many respects was a rival preferred by her mother. She is the only patient whom I have seen to whom an animal has played the rôle of sibling and who has in many respects identified herself with a cat. She constantly dreams of a mother cat and kittens, of kittens being born in the toilet and of poor, starved, thin, homeless kittens. When she passes a stray cat on the street she is overcome with a desire to take it

home and mother it. The next step in the story is she now felt the weight lying on her chest was a cat. This was in no sense an hallucination. It was a fantasy. She continued to feel breathless and then told me she felt the cat was inside her chest. After awhile the feeling of substernal oppression passed and the patient then complained of a lump in her throat which made her feel as if she were strangling. This in turn passed off and she again breathed quietly and easily. A few days before this experience she told me of a dream in which some birds fell over as if dead, whereupon little birds appeared to hop out through the bigger birds' chest walls. She has a constant fear of death as she has of sexuality and childbirth which are closely associated in her mind with the idea of dying. Paradoxically enough she has a strong suicidal drive, as if indeed she wanted to jump into the lake to escape the rain.

The feeling of being unable to take a deep breath, i.e. dyspnea, is commonly encountered in anxiety states, indeed the sensation itself undoubtedly gives rise in some individuals, though not in all, to feelings of anxiety. Dyspnea is properly speaking a subjective symptom, not an outward sign. It has been defined by Means [3] as "the *consciousness of the necessity for increased respiratory effort.*" It will occur, as Means says, whenever the respiratory mechanism cannot with ease function to the extent that bodily processes require. It is an interesting fact that consciousness is directed to the thorax or diaphragmatic region while the cause of the difficulty may be either in the lungs or in some far distant part of the body. The most common cause of dyspnea is physical exertion.[4] The increased pulmonary ventilation is then the result of increased metabolism. This does not lead to any distressing symptoms until the demand for oxygen and elimination of carbon dioxide is greater than the lungs can perform with comfort. Thyrotoxicosis and febrile states may produce a similar type of dyspnea due to excessive metabolic demands. A different mechanism, yet one occasioning the same subjective sensation, may result from anemia, anoxemia, changes in the acid-base equilibrium of the blood and tissues, or decrease in cardiac output. In each one of these the disability and distress are referred to the breathing apparatus—just as it is in those conditions such as pneumonia, congestive heart failure, pulmonary fibrosis, emphysema, and bronchial asthma where the fault actually lies in decreased efficiency of the pulmonary bellows and is associated with reduction in vital capacity and pulmonary elasticity. The localization of respiratory distress in the region of the diaphragm even when the pathological lesion is remote is an interesting phenomenon. It seems almost like a conditioning or like a projection; as if the patient were saying "I can't breathe easily, therefore there must be something wrong in my chest." Perhaps, however, the sensation is experienced where it is because existing nervous pathways can convey it nowhere else. It is apparently a well canalized one, for many sensations of excitement and anxiety are felt in the same zone. Those of us who were in the war saw numerous cases of so-called *neurocirculatory asthenia* or *disordered action of the heart* in which shortness of breath played a prominent part. I remember an enormous black negro in a white night shirt sitting up in bed and breathing at the rate of 120 per minute with nothing abnormal disclosed

on the physical examination to account for such a disturbance. In some of the more severe cases of this sort pronounced cyanosis appeared and even collapse from what was thought to be exhaustion of the respiratory center. Very often, however, during sleep or hypnosis the respiratory rate returned to normal. That the condition was associated with an acute anxiety state with suppression of affect is not improbable. The physiological explanation given for this type of rapid and shallow breathing is that " the normal reflexes are preternaturally hypersensitive." [5] Breathing is, to be sure, only partially controlled by reflex mechanisms. In the control and regulation of the rate and depth of breathing its twofold character is again in evidence. Its regulation is partly nervous, partly chemical. It is partly reflex, partly under voluntary control. In this respect it differs somewhat from the other two great vegetative systems, the cardiovascular and the gastrointestinal, and resembles more nearly the mechanism of the sexual function. It is perhaps because it represents a meeting point of conscious and automatic activity that it so easily lends itself to an expression of emotional tensions and disturbances.

The impulse to breathe arises in the so-called respiratory center which is located somewhere in the medulla oblongata about at the level of the *striae acousticae*. This locus was first identified in 1811 by Le Gallois.[6] The center apparently discharges at a constant slow rate sending impulses to the intercostal muscles along motor fibers of the spinal nerves and to the diaphragm through the phrenic nerves. Recently these rhythmically discharging impulses have been studied and graphically recorded in the cat by Adrian.[7] Their origin is of course unknown but they appear to resemble the so-called Berger waves from the cerebral cortex. The activity of the center is exquisitely sensitive to changes in the H-ion concentration of the blood and the lymph which bathes it and perhaps specifically to CO_2 and also, of course, to oxygen want. Since oxygen want constitutes a profound threat to the integrity of the organism, more especially to the functioning of cortical and autonomic centers, it is probable that the feeling of anxiety and panic induced by asphyxial states serves as a danger signal to the individual. We are familiar with Freud's concept of anxiety as a danger signal. Whether anxiety, more specifically neurotic anxiety, is related to anoxemia as Deutsch [8] has intimated, we do not know. This is a problem which could be investigated. McFarland and Barach [9] have recently exposed a group of psycho-neurotic individuals to low partial pressures of oxygen. They found that these patients tolerated low atmospheric oxygen less well than a control group. There is in all probability a high degree of individual variation in this. Some individuals respond to anoxemia and shortness of breath with feelings of anxiety and others do not, perhaps depending upon their capacities to function physiologically at low oxygen tension, and perhaps also upon their earlier conditioning in respect to these states. I shall not deal here with work which has been done on the effects of low oxygen tensions on sensory

reaction times, muscular coördination, discriminative judgments, etc. I refer to observations made with rebreathing apparatus and low pressure chambers especially in relation to testing of fliers; also to observations made at high altitudes. The recent International High Altitude Expedition to the Andes [10] has furnished some data which may make it possible to predict which individuals will tolerate low oxygen pressures well and which will not. This, to be sure, is a different problem from the one to which I have already referred, i.e. the relation of anxiety to anoxemic states.

Chemical stimuli determine to what extent inflation and deflation will occur but probably have little influence upon the frequency of respirations. The latter is governed by a sensory reflex mechanism first described in 1868 by Hering and Breuer.[11] Afferent sensory impulses from the lungs reach the center by way of the vagus nerves. Their existence has been demonstrated not only by cutting and freezing experiments which elicit typical slow, deep, so-called vagal, breathing, but action currents of afferent vagal impulses synchronous with respiration were demonstrated by Einthoven.[12] The vagi, as the great afferent nerves of the lungs, serve in the complicated apparatus to protect them against the effects of excessive distention or collapse. They inform the respiratory center of movements of air currents and the position of the lungs, and reflexly check the depth of breathing. The chemical factors therefore control the total pulmonary ventilation; the afferent vagal impulses control the rhythm of breathing. I have not dealt here with the less understood function of intrinsic sympathetic pulmonary and bronchial ganglionic plexuses. In general, as Means [13] says, the nervous control of breathing may be expected to secure for us that respiratory type which in accordance with the local condition in our chest or abdomen, may most comfortably supply the ventilation required for the gas exchange which our general bodily processes may happen at any time to demand.

I have described this subject of the control of the depth and rate of breathing for two reasons: First, because a recent attempt has been made by Alexander and Saul [14] to relate the form of the respiratory curve to certain personality traits; second, because a discussion of the nervous control of respiration leads naturally to a consideration of asthma in which occurs a reflex stimulation of the smooth muscle of the bronchial wall through vagal broncho-constrictor fibers and in which an emotional element plays a rôle of major importance.

Regarding Alexander and Saul's work, I have, to be sure, seen only an abstract. They believe they have shown that a certain correlation exists between the form of the respiratory curve and certain libidinal trends. That the respiratory curve is influenced by anxiety, by tension and even by a specific personality factor, I am quite ready to believe. But to establish the fact that a correlation exists between the form of the respiratory tracing and specific instinctual drives would require a large statistical material. Alexander and Saul are quite aware of this. They present their conclusions with

appropriate caution and modesty. I am glad to learn that Deutsch and Finesinger [15] are also engaged in investigating this problem with particular attention to the influence of induced affective states on the form of the respiratory curve.

Turning now to the subject of asthma I should like to summarize certain findings concerning it in the psycho-somatic field. That asthmatic attacks are often closely bound to certain specific life situations is now common knowledge. Psychotherapy, after other methods of treatment have failed, has in some individuals brought about the disappearance of Charcot-Leyden crystals, Curschmann's spirals and even of eosinophilia from the sputum and blood. I refer to a series of cases reported upon by Moos.[16] Hansen's [17] investigation led him to the view that the psychological situation has much to do with the reactivity which some patients exhibit to specific antigens to which they are sensitive. Moreover he says: "I cannot escape the impression in many cases that not infrequently a seemingly causal psychic alteration may be only coördinated with the somatic reaction, and that both are dependent on a mysterious third factor that escapes our detection. It seems to me, for example, that not infrequently certain asthmatic individuals show to a more or less marked degree symptoms of manic-depressive disease, and that asthmatic attacks predominate in attacks of depression."

Support of Hansen's contention is furnished by Saxl [18] who reports the case of a patient, who had suffered from migraine since early youth and had been subject to fluctuations of mood. He was seized with attacks of bronchial asthma during the involutional period. Some years later, perhaps precipitated by a further psychic trauma, he developed a manic-depressive state in the course of which five exacerbations were observed. An attack of asthma subsided each time previous to the acute exacerbation of psychosis, only to return with its disappearance. Oberndorf [19] reports the analysis of an asthmatic in which he believes it was shown (1) that psychological stimuli set the attacks in motion; (2) that the so-called specific allergic determinants had nothing to do with the attacks; and (3) that after treatment the asthmatic attacks were substituted by emotional outbursts quite like manic episodes. The patient, after treatment, ate chicken, corn and cabbage freely and was able to tolerate the presence of dogs and cats. To all of these she exhibited positive skin reactions. Fenichel [20] has attempted a more detailed description of the psycho-dynamic situation in asthma—stating that asthma is not an hysterical conversion symptom and that the asthmatic between attacks behaves like an obsessional neurotic. In his book in which he devotes some ten pages to the subject, Fenichel places asthma between stuttering and psychogenic tic. He assumes the existence of intrinsic respiratory eroticism and reduces the psychological process in asthma to a formula, of the validity of which I am on principle rather skeptical. As to the therapy of asthma, Fenichel believes that the analyst's task is the radical treatment of the pregenital psychological structure which he believes underlies the

symptom. Quite properly Fenichel also mentions the intimate relationship that exists between anxiety and the function of respiration. In this connection he discusses the views of Hárnik [21] who finds the fear of suffocation a widespread phenomenon and relates it to castration anxiety of which he believes it to be a distorted expression. One of his patients, for example, imagined that the analyst might cut off his air supply by means of scissors. The second point derived from Hárnik is that fear of being smothered underlies every fear of death and is in general the most archaic content of anxiety. He believes that this feeling, which may be experienced at the time of suckling, remains connected unconsciously with every later experience of a dangerous situation. I have at present under observation a young man who develops deep gasping respirations whenever his anxiety is aroused by matters touching on his social or economic inadequacy. All his life he has suffered from an acute sense of anxiety in any situation in which there was any suggestion of smothering—for example, if any one in fun would put a pillow on his head. The intimate relationship which exists between anxiety and respiration suggests the possibility that the constant variations in respiratory function are based in part, at least, upon constant unconscious responses to anxiety. It is my personal observation that the sensation which we recognize as anxiety is felt in the lower anterior thoracic wall and presents itself to us as a feeling of being unable to inspire freely. I suspect that it may arise in kinesthetic impulses from the diaphragm which may be related to its tonus. Christie [22] believes that the incidence of respiratory disorder in neurosis is much greater than is generally supposed and that tracings taken by means of an ordinary recording spirometer are of value in the diagnosis and differentiation of certain types of neuroses. His cases fell into two groups: anxiety neuroses with irregular shallow type of respiration, and conversion hysterias, with a tendency to hyperventilation. This latter occurrence is consistent with sighing respiration which I have mentioned and to which Baker [23] has recently drawn attention. A thorough investigation of pulmonary volumes would be of interest in this connection.

As might be expected, the idea of "birth trauma" has found its way into discussion of the etiology of asthma. Freud has challenged the value of this hypothesis admirably in his recently translated "Hemmung Symptom und Angst." May I quote: "The principal objection to be raised against it, however, (i.e. the birth trauma) remains the fact that it hangs in mid-air, instead of being based upon verified observation. For no trustworthy investigation has ever been carried out to determine whether difficult and protracted birth is correlated in indisputable fashion with the development of neurosis—indeed, whether children whose birth has been of this character manifest even the nervousness of earliest infancy for a longer period or more intensely than others. If the assertion is made that precipitate births, those easy for the mother, may possibly have for the child the significance of a severe trauma, then *a fortiori* it would certainly be necessary that births

resulting in asphyxia should produce beyond any doubt the consequences alleged. It seems an advantage of the Rankian etiology that it postulates a factor capable of being checked empirically; but as long as such a check has never actually been undertaken, it is impossible to estimate its real value." There is of course no reason why such an investigation could not be undertaken with special reference to asthmatics.

Closely related to this psychoanalytical hypothesis are certain recent physiological studies made in England by Barcroft [25] and in this country by Rosenfeld and Snyder [26] at the Johns Hopkins Medical School. These investigators have studied intra-uterine fetal respiratory movements. Barcroft's work began several years ago with an effort to answer the question "What sets off the birth process?". By a study of arterial oxygen saturation of goat fetuses he believes he has demonstrated increasing anoxemia as the fetal circulation no longer supplies the needs of the growing organism. A point is reached when, as Barcroft [27] put it: "It gets so stuffy that the fetus moves out." If this is true then the amniotic sac is perhaps not the Nirvana which some psychoanalysts have led us to believe. States of tension and frustration may already be experienced in utero, and birth is not into a vale of tears, nor the prototype of all subsequent traumata, but rather a happy release. Barcroft demonstrated cinematographically the existence of rhythmic respiratory movements in fetal sheep and goats beginning as early as the thirtieth day, but curiously enough disappearing during the course of gestation. The occurrence of intra-uterine respiratory movements is not a newly discovered fact, having been observed by Preyer [28] as long ago as 1885. It received scant attention, however, until recently. Rosenfeld and Snyder have improved upon Barcroft's technic by eliminating the use of general anesthetics which they discovered depressed or completely inhibited intra-uterine respiration in the fetuses. Their observations were made on rabbits after section of the lumbar cord under local anesthesia. Fetuses within the intact uterus exhibited spontaneous respiratory movements characterized by rhythmic excursion of the thorax and abdomen. Although shallower, they resemble qualitatively the respiratory movements observed after birth. There is great variation in respiratory activity among different fetuses in the same uterine horn; some may be quiescent, others respiring at independent rates up to 60 per minute. No evidence was found that stimulation of fetal respiration occurs from oxygen want nor indeed from the administration of CO_2 to the mother. They regard the onset of post-natal respiratory activity not as an event initiated abruptly at birth but rather as a transition from the type of respiratory movement discernible during intra-uterine life. They do not support the view of Barcroft that the first breath of a newborn animal is caused by oxygen want. To be sure cyanosis often occurs in the newborn as the result of prolonged labor and the use of anesthetic agents in the mother—but, as has been said, whether this constitutes a psychic trauma to the child is still unknown. In the

absence of such knowledge it hardly seems fruitful to try to explain the disordered breathing of an asthmatic attack in terms of regression to the postnatal state.

The condition of oxygen want naturally leads us to a consideration of pneumonia. There is more accurate knowledge about anoxemia in pneumonia than in almost any other disease. In spite of this, I know of no serious effort to correlate psychic changes in patients suffering from pneumonia with changes in the degree of anoxemia, though there have been comments on the decrease of restlessness and subsidence of delirium during oxygen therapy.

That the morbid picture is much influenced by anxiety states—fear of suffocation—fear of death, I have no doubt. A careful study of the events leading up to the infection would be of interest, as well as a study of the productions in delirium and the effects of more active suggestive therapy. C. Widmer [29] was aroused to an interest in this problem by events occurring after a fire in the Swiss hamlet of Tamins in which eight of those engaged in fighting the fire after drenching and exposure came down in from one to two weeks with attacks of severe pneumonia initiated by chills and soon followed by high fever and delirium. The patients lived at great distances from each other so that the doctor could not visit them all. In order to protect them from exposing themselves during their nocturnal delirium he was led to adopt the emergency measure of getting the patients out of bed at night and having them dress. He found to his amazement that the active delirial symptoms disappeared and that there occurred simultaneous clinical improvement. Apparently this experience caused him to investigate in the succeeding 10 years some of the psychological disturbances which he regarded as characteristic of pneumonia and which in his opinion were not related to the deliria of high fever nor to toxic exhaustive states. He found alteration in what might be called the integration of perception: a disturbance in the recognition of place, position, space, distance, division, rhythm, number, movement. This, according to Widmer, is the basis of the delirial state which may be present early in the disease and may be unrelated to the height of the fever or to any evidence of meningeal involvement. Since the patient's memory for recent events and his superficial contact with his environment may be unimpaired the existing delirium may at first escape detection. Widmer essayed to correct this state of confusion not by direct conscious psychotherapy since he found his patients lacking in insight and quite inaccessible, but by the expedient of getting them out of bed. Sometimes he had them sit in rocking chairs for as much as from four to six hours a day, even letting them take a few steps. By these and various other maneuvers he attempted to bring them back to a more normal relationship to their environment. He states that the procedure far from doing the patients harm led to normal sleep, to disappearance of delirium, to improvement in blood pressure and to moderation of toxic manifestations. Widmer's observations, of course, need corroboration, although it would

require some temerity to repeat them in this country where it is customary to keep the convalescent from pneumonia at rest in bed for at least a week after his temperature has returned to normal. Still I think it is apparent that these experiences if they are correctly reported are not without interest.

In the beginning of this paper I spoke of the unwisdom of advocating such concepts as *psychogenic versus organic* as applied to the etiology of disease. It is my belief that any disease from hysteria to carcinoma or better any diseased individual may be studied legitimately and with profit by methods both psychological and organic. What we discover with these methods will be different sets of facts; in the one instance psychological facts, in the other, facts which have anatomical, chemical or physiological bearings. To correlate these will always be difficult—perhaps will be looked upon for the present as a *tour de force*. But such efforts seem to me to be of value. Our attitude toward disease is changing. It is no longer satisfactorily explained as a catastrophic invasion by noxious agents, a belief handed down to us not by bacteriologists alone but by our more primitive animistic ancestors. We know now that it requires more than the tubercle bacillus to make a man tuberculous, more than a specific antigen to produce an asthmatic attack and more than pneumococci to precipitate an attack of pneumonia. The other ingredient in the disease state was then thought to reside in the " reaction of the host," by which was meant in his humoral and immunological defenses. There is now a growing body of evidence which leads to the belief that psychic influences as well play an important part in the process of falling ill, and that disease be it infectious, allergic, functional, organic or degenerative has its developmental history in which the whole personality is involved. To cultivate this field we must create new methods of personality study aided by the insight which psychoanalysis has given us.

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CASE REPORTS

MARKED UREMIA WITH RECOVERY; REPORT OF A CASE*

By R. O. Bowman, Ph.D., and S. Wolpaw, M.D., *Providence, Rhode Island*

Case Report

J. F., a 29-year-old white woman, was admitted to the Surgical Service of the Cleveland City Hospital on September 12, 1933.

According to the patient's history her last menstrual period had occurred on July 8, 1933. Having missed her August period and believing herself to be pregnant she had attempted to produce an abortion by the use of various oral medications, the exact nature of which we were unable to determine. Failing in this attempt an abortion was induced on September 7, by packing the vagina with gauze. The pack was removed after one day and was followed by rather profuse vaginal bleeding. Twenty-four hours later the patient had a severe chill and felt feverish. She began to vomit rather copiously and it was called to her attention that her eyes had become yellow in color. These symptoms became increasingly severe until the time of her admission to the hospital.

The past history was negative except for four induced abortions during the past eight years, several of them followed by chills and fever. The patient had four living children.

Examination showed the patient to be well-nourished and acutely ill. The skin and sclerae were definitely jaundiced. There were no visible petechiae. The heart and lungs were normal. The blood pressure was 110 systolic and 60 diastolic. The abdomen was negative except for the liver which was just palpable at the costal margin. The spleen was not palpable. Pelvic examination revealed the cervix to be lacerated but firm. The uterus was enlarged, boggy and in a posterior position. There was tenderness in both fornices on motion of the cervix. There was no peripheral edema and the reflexes were physiological.

The temperature on admission was 37.8° C., the pulse 90, and the respirations 20. The blood urea nitrogen was 183 mg. per 100 c.c., the creatinine 18.6 mg. per 100 c.c.; the carbon dioxide combining power 20 volumes per cent; the icteric index 63; and the hemoglobin 65 per cent (Sahli). A blood Wassermann was negative.

The clinical impression on admission was that of an incomplete abortion, and a toxic hepatitis and nephrosis with uremia. The latter lesions were attributed to the ingestion of an unknown drug.

Two days after her admission to the hospital the patient signed her release and was discharged against advice.

The patient was readmitted, this time to the Medical Service, on September 23, 1933, eleven days after her original admission. Her condition during this interval had become progressively and rapidly worse. At this time the history was obtained from the patient's husband that the abortion on September 7, 1933 had been attempted by placing two bichloride of mercury tablets against the cervix and packing the vagina with gauze. Samples of the oral treatment (Savatan capsules in their original box, several of which were missing and one broken in half) were also submitted.

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From Cleveland City Hospital, Cleveland, Ohio.

Date	9-13-33	9-14-33	9-15-33	9-23-33	9-25-33	9-29-33	9-30-33	10- 5-33	10-10-33	10-16-33	11- 1-33	11- 7-33	11-14-33	12- 9-33
BLOOD														
Urea N, mg./100 c.c.	183			352	262		195	77	21.9		10.3	9.1	10.6	19.8
Creatinine, mg./100 c.c.	18.6			24.3	16.5		14.6	5.2	2.3		1.3		1.9	2.2
CO_2 comb. power, vol. %	20			14.5	13.6		25.8	32.0	44					
Uric Acid, mg./100 c.c.				14.4				7.2	3.7					
Cholesterol, mg./100 c.c.								125	140			67.3		
Sugar, mg./100 c.c.	106			85	138		152							
Plasma inorg. P., mg. 100 c.c.									2.5					
Icteric Index	63	53						5.5			4.8			
Hgb., gm./100 c.c.									4.6		7.6	10.3		
R.B.C., millions	2.95			2.53						1.91				3.66
W.B.C., thousands	14.4			11.8						6.9				
Hgb., (Sahli)	65%			60%						40%				60%
URINE														
Reaction		acid	acid	acid	acid	acid	acid	acid	acid	acid	acid		acid	
Sp. gr.		QNS	1.018	QNS	1.010	1.010	1.010	1.006	1.004	1.006	1.008		1.012	
Albumin		+++	+++	+++	++	+	0	0	0	S Tr	0		0	
Sugar		0	0	Tr.	0	0	0	0		0	0		0	
Casts		hyaline	hyaline	0	0	0	0		0	0	0		0	
W.B.C.		+	+	++++	++++	++++	++	+	+	+	+		0	
R.B.C.		rare	rare	++	++	++	++	rare	0	0	0		0	
P.S.P. (2 hr. excretion)			0%										45%	
Urea clearance													63%	36.2%

Examination at this time revealed the patient to be deeply jaundiced. She was extremely ill, toxic, disoriented, and had a watery and bloody diarrhea. The physical findings were not of great significance. The respirations were regular and very deep in character. The liver was not palpable. There was slight bilateral costo-vertebral tenderness. The temperature was 37° C., the pulse 90, and the blood pressure 110 systolic and 64 diastolic. There was no pericardial friction.

The laboratory findings on the day of this admission showed that the blood urea nitrogen was 352 mg. per 100 c.c. (checked); the creatinine 24.3 mg. per 100 c.c. (checked); the uric acid 14.4 mg. per 100 c.c.; and the CO_2 combining power 14.5 volumes per cent.

The clinical impression on this admission was uremia due to bichloride of mercury poisoning, with hepatitis and nephrosis.

During the 10 days after admission the patient's condition remained critical. She was disoriented the greater part of the time. Her diarrhea continued with four to seven stools daily. Her urinary output when measurable varied between 250 c.c. and 750 c.c. a day. She developed a bilateral suppurative parotitis which required incision and drainage, and a bilateral acute otitis media which required myringotomy. Treatment consisted of usual routine measures for bichloride of mercury poisoning; 4000 c.c. of normal saline solution daily by clysis, imperial drink, sodium thiosulfate, and glucose given by mouth and intravenously. The anemia which became rather marked responded well to a 50 per cent solution of ferric and ammonium citrate. After two weeks her improvement was slow but steady and there were consistent changes in the urinary and blood chemistry findings. On 11–14–33 her blood urea nitrogen and creatinine were normal and the urine negative, with low specific gravity. Phenolsulphonephthalein excretion was 45 per cent in two hours and the average of two Van Slyke urea clearances (maximum clearance) was 63 per cent. A Mosenthal test run the next day showed average specific gravity of 1.014 for the day and the same figure for the night specimen. On 12–9–33 her blood urea nitrogen had risen slightly to 19.8 mg. per 100 c.c. and a repeat urea clearance determination was 34 per cent of standard and 39 per cent of maximum. She was discharged from the hospital on 12–11–33, three months after her first admission, having nearly regained her normal weight. The chart gives the blood and urine findings during her hospital stay.

On 9–13–35 she was again admitted on the Obstetrical Service of City Hospital and was delivered uneventfully of a normal full-term child. Her post-partum course was not remarkable. Physical examination at this time showed no significant findings. Her blood pressure was 102 systolic and 64 diastolic. The urine was negative for albumin, sugar, cells and casts. The specific gravity was 1.008. The patient left the hospital by release before kidney function studies could be performed.

The patient was seen personally in February 1936, two and one-half years after her original admission. She refused further follow-up studies but stated that she had been quite well and able to do all of her own housework.

A search of the literature has failed to reveal a case of such marked uremia with recovery, and we feel that recovery here has been adequately proved by the ability of her kidneys to withstand pregnancy. Selman and Lenigar,[1] from this hospital, have reported a case of asthmatic shock which recovered after developing a blood urea nitrogen of 142 mg. per 100 c.c. and creatinine of 15.4 mg. per 100 c.c. Our case showed a much more severe blood picture, while the blood urea nitrogen is the highest seen by us in some 25,000 determinations.

We have no proof that this is a case of mercury bichloride poisoning. Only one sample of urine of less than 100 c.c. was examined for mercury on 9–26–33 and none was found. One would not expect to find it in such a small quantity of urine, particularly since the absorption and excretion from the vagina would

both be rapid, and small amounts of mercury are more toxic by this route. This same sample was negative for leucine and tyrosine crystals. Montzka [2] has reviewed poisoning with mercury by the vaginal route and reports a fatal case. Mintz [3] has reported that 7.5 grains of mercury bichloride were fatal. The history here indicates double this dose was used.

The other possible etiological factor is the Savatan. The Bureau of Investigation of the American Medical Association has kindly supplied the information that Savatan contains the ecbolic oils of tansy, mint and apiol.[4] Brenot,[5] whose original article we were unable to obtain, has reported a case of fatal poisoning with apiol with intestinal symptoms, icterus and uremia, but the dose which is toxic (0.6 to 0.8 gm.) would be improbable here since only eight and a half of the capsules had been taken. One of the important toxic actions of this drug is on the heart, yet at no time did this patient show any cardiac abnormalities. The hepatitis, which occurred rather early to be due to mercury, might have been caused by the ecbolic oils.

SUMMARY

A case record is presented of a patient with marked kidney insufficiency probably produced by mercury bichloride per vagina, who recovered sufficiently on routine treatment to undergo a normal pregnancy two years later.

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REPORT OF A CASE OF STATUS ASTHMATICUS WITH AUTOPSY *

By JOSEPH R. WISEMAN, M.D., F.A.C.P., *Syracuse, New York*

CASE REPORT

Mrs. E. H., a housewife, aged 40, entered the University Hospital, October 16, 1935, complaining of severe asthma.

Her mother, aged 77, has arteriosclerosis. Her father died at 50 of heart trouble. One brother is living and well; no sibs have died. She has four living children, one of whom has diabetes for which insulin is taken; one child died at four of nephrosis. No allergic family history could be obtained. The patient lived in Syracuse, New York all of her life except for two trips to Florida in 1925 and 1927. In childhood she had measles, mumps, and varicella; jaundice in 1915, pleurisy twice (1918 and 1934), mild scarlet fever in 1927 with no complications. A goiter had been present for 27 years. There had been some swelling of the ankles for 11 years, most

* Received for publication November 5, 1936.

noticeable at night. Since the attack of scarlet fever in 1927 she had been moderately short of breath.

Previous hospital admissions: 1919, Laparotomy—gall-bladder found to be normal, appendix removed. 1934, Acute upper respiratory infection—asthma. 1935 (March): Acute upper respiratory infection—asthma. 1935 (May): Severe asthma.

During her stay at the University Hospital in 1934 the following observations were made: Hemoglobin 93 per cent, red blood cells 4,900,000, white blood cells 7,500, polynuclears 59 per cent, lymphocytes 33 per cent, large mononuclears 5 per cent, eosinophiles 3 per cent. Other eosinophile counts were 0, 1 per cent and 5 per cent.

The patient attended the Cardiac Clinic at the Syracuse Free Dispensary from July 3, 1934 to April 16, 1935. Numerous observations of the vital capacity, blood pressure and heart rate gave the following average readings: vital capacity 2,475 c.c., blood pressure 126 systolic and 85 diastolic, heart rate 86. The heart outlines were within normal limits and the sounds were clear. She was discharged with a final diagnosis of "No organic heart disease—bronchial asthma."

She came to the Allergy Clinic at the Syracuse Free Dispensary July 31, 1934, and was under my observation until her last illness. Her first asthmatic seizure occurred in September 1929, two years after an attack of scarlet fever. For five years she has taken ephedrine every night and often has had to sit up in a chair. The asthma was worse in winter and in rainy weather. In the summer of 1934 from June to August she had considerable sneezing.

More than 80 intracutaneous skin tests gave positive reactions to house dust, ragweed, feathers, wheat, lima bean, lamb and cocoa. She was given advice as to environmental precautions and the elimination of suspected foods, and was treated by injections of house dust, ragweed and mixed stock respiratory vaccine. At her visits to the clinic she appeared cheerful and optimistic and seemed to show some improvement but upon close questioning admitted one or more attacks of asthma requiring ephedrine practically every night. At times her daughter gave her epinephrine by hypodermic. She was placed upon a Rowe elimination diet for five weeks without relief. On May 17, 1935, she had a severe attack of asthma; the tongue was said to be swollen and the face and hands blue. She had to be carried downstairs in a rocking chair and was taken to the Onondaga General Hospital where she remained one week.

Late in September 1935 she developed an acute upper respiratory infection which kept her in bed four days and caused a marked increase in the number and severity of the asthmatic attacks. She became exceedingly weary and remained propped up in bed all of the time. A hypodermic of epinephrine had always helped her but on October 16, she was unable to obtain relief, even from 1 c.c. She became faint and was sent by ambulance to the University Hospital, where she was placed on the medical service of Dr. W. D. Ayer.*

Admission examination: A refined appearing woman of good nutrition and development, sitting up in bed, breathing with great difficulty, using all of the accessory muscles of respiration. Pupils are equal and react to light and accommodation. Some nasal discharge. A few dental cavities. Throat injected, tonsils cryptic. Small goiter. Lungs hyperresonant and filled with wheezing râles. Heart enlarged to left with systolic and diastolic murmurs in the mitral area, and a diastolic blow at the left border of the sternum. Sounds are regular in force, rate and rhythm. Blood pressure 150 systolic and 90 diastolic. Abdomen soft, operative scar present. Liver and spleen not felt. Reflexes hyperactive.

During the five days of her hospital stay she presented the picture of continuous asthma which resisted all medication. She took very little fluid by mouth and practically no food. She went practically without sleep except for a few brief intervals

* I am indebted to Dr. W. D. Ayer and to Dr. E. C. Reifenstein, physician in chief, for the privilege of using the records of the University Hospital.

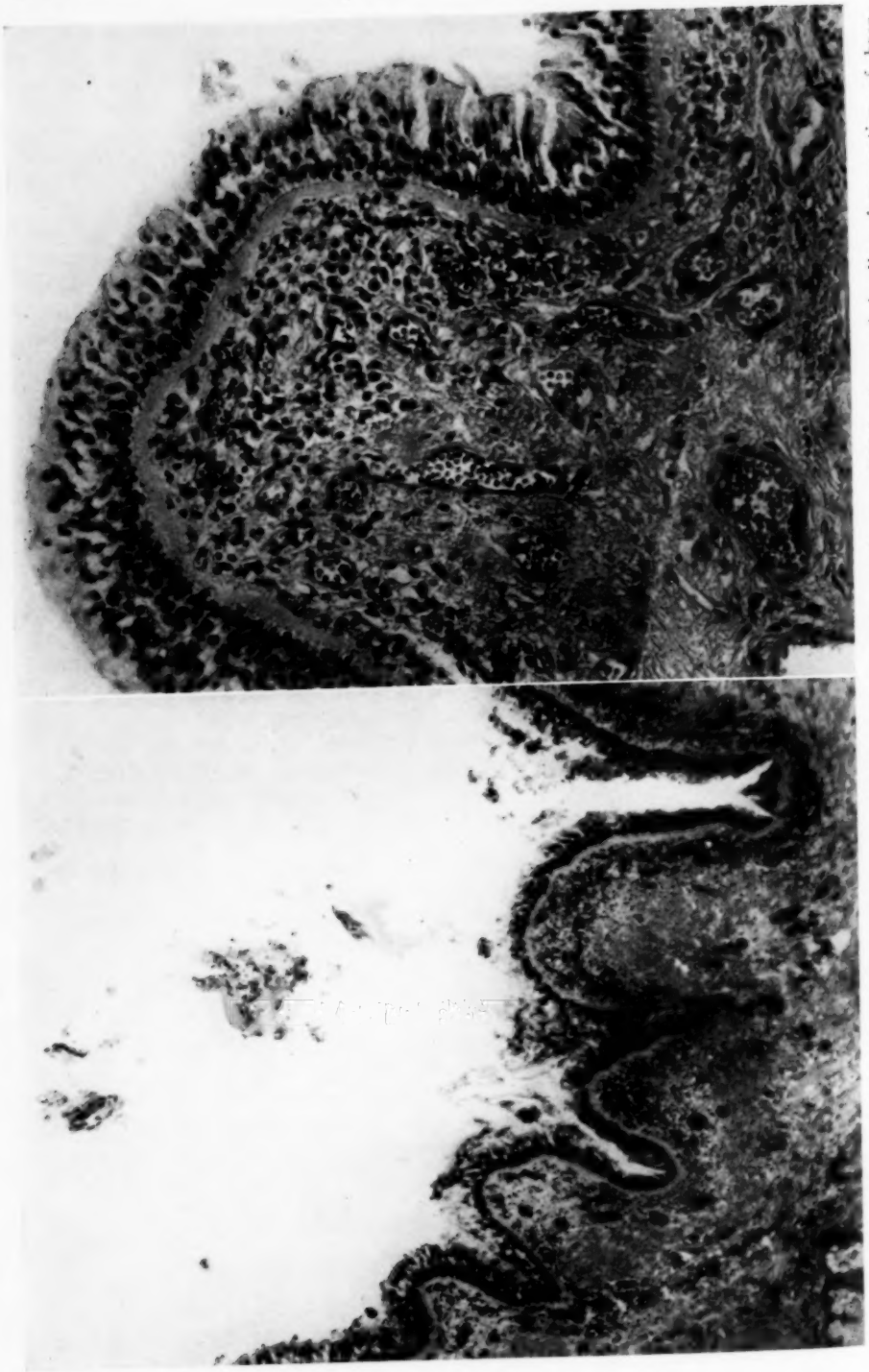

FIG. 1. Large bronchus (low power and high power). Infolding of mucous membrane. Thickening and hyaline degeneration of basement membrane. Inflammatory reaction and dilated vessels.

when she became drowsy after a hypodermic of morphine. Ether and oil per rectum were not well retained and had little effect. Continuous oxygen therapy by tent was of little service. The diastolic murmurs noted at entrance were not heard thereafter. The pulse became more rapid, the skin cyanosed, the ankles edematous and the abdomen distended. Unconsciousness supervened, the temperature reached 108° ante mortem and the patient died from exhaustion on October 21, 1935.

She received iodide by mouth and vein, calcium gluconate, inhalations of epinephrine 1–100, ephedrine gr. 3/8 with amytal gr. 3/4, morphine by hypodermic gr. 1/8 to 1/4 with and without atropine, 14 doses, a total of 2 5/8 grains, digitalis 9 doses, 13 1/2 grains. At first 1 c.c. doses of epinephrine were given by hypodermic, later 0.5 c.c. was administered at intervals of 15 to 30 minutes. In all 114 doses were given, about 2 1/2 oz. in five days. Until just before death the temperature had varied from 98.6° to 101°, the pulse from 82 to 120, and the respirations from 20 to 30.

Following are the essential features of the autopsy by Dr. Robert O. Gregg and Dr. J. Howard Ferguson: Body is that of a fairly well developed, well nourished, middle-aged woman. There is apparently slight distention of the abdomen. There is slight edema of the ankles.

Pleural Cavities: The lungs fill the cavities and meet across the midline when the thorax is opened and cover nearly the entire pericardium. There are no adhesions and no free fluid.

Thyroid: The thyroid is symmetrically enlarged, but the trachea is not depressed.

Mediastinum: Without evident lesion.

Pericardial Cavity: Contains approximately 10 c.c. of clear amber fluid. Pulmonary artery opened in situ is without evident lesion.

Heart: Weight 275 gm. The right auricle is markedly dilated and filled with fluid blood. The ventricles are contracted. The auricular appendages are without evident lesion. The tricuspid, pulmonary and aortic valves are without evident lesion. There is some thickening along the line of closure of the mitral valve, particularly on the anterior cusp. The coronary arteries show a slight amount of yellowish thickening and seem to be soft throughout their entire extent. On section of the myocardium the muscle is deep reddish brown in color and rather firm in consistency. There are two small areas of whitish softening in the anterior wall of the left ventricle.

Lungs: Weight of left 260 gm. Weight of right 260 gm. On section the lungs seem much more crepitant than usual. On pressure there seem to be scattered diffusely throughout both lungs numerous air-containing spaces up to 1/2 or 1 cm. in diameter. The bronchi throughout both lungs, particularly in the lower lobes, are filled with thick tenacious mucus. The lungs are grayish pink in color throughout. Vessels and bronchial lymph nodes show nothing unusual.

Liver: Weight 1500 gm. The liver substance is yellowish brown in color and somewhat firmer in consistency than usual. There appears to be a minimal amount of scar tissue throughout the entire liver structure.

Kidneys: Weight 260 gm. The kidney substance is reddish brown in color throughout except for one area of rather grayish white color and firm consistency in the cortex of the left kidney. This area is approximately 1 cm. in diameter and extends to the capsule. The capsules strip easily. The cortex and medulla have the usual relationship.

Adrenals: Show nothing unusual.

Aorta: Shows a minimal amount of yellowish thickening.

Anatomical Diagnosis: Bronchitis. Marked pulmonary emphysema. Probable infarct of kidney.

Microscopical Diagnosis: Heart: Some fatty and Zencker's degeneration of myocardium. Slight fibrosis. *Liver:* Slight fine scarring in areas. *Kidneys:* Infarction

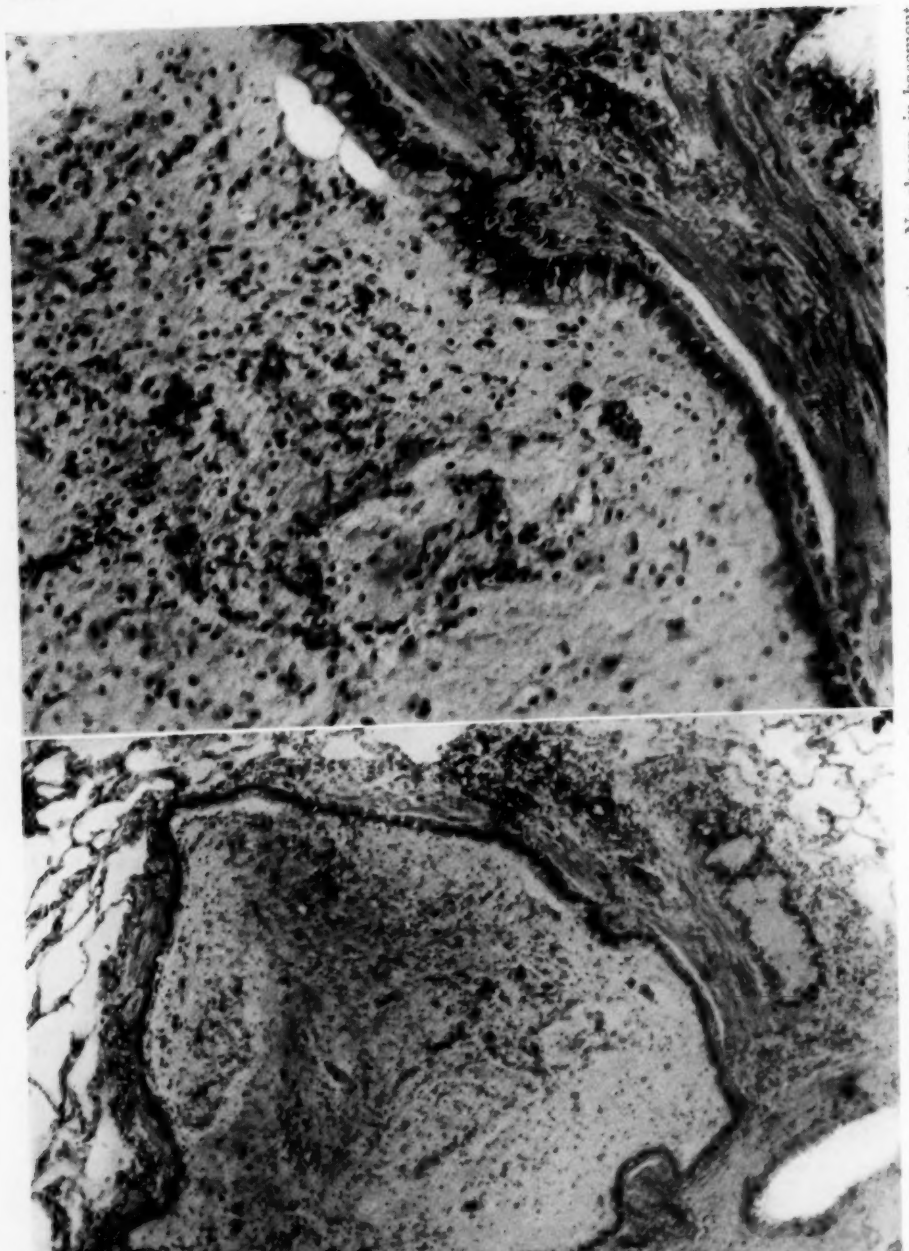

FIG. 2. Small bronchus (low power and high power). Mucous plug filling lumen. Slight inflammatory reaction. No change in basement membrane.

with extensive, capillary thrombosis of glomeruli, marked tubular degeneration. *Lungs:* Generalized emphysema with scattered areas of slight fibrosis with some infiltration of lymphoid cells. The larger bronchi show some infolding of the mucous membrane. In some areas the goblet cells are more prominent than usual. Other areas do not appear unusual. The basement membrane throughout shows rather marked thickening and hyaline degeneration. In the sub-epithelial connective tissue there is a diffuse infiltration of leukocytes consisting of lymphoid cells, plasma cells, and eosinophiles in about equal proportions. The small blood vessels in this area are unusually prominent. There are scattered capillary hemorrhages. The mucous glands are prominent but otherwise not unusual.

The smaller bronchi and bronchioles show less infolding of the mucous membrane. The basement membrane shows only scattered areas of thickening and very little hyaline degeneration. There is some infiltration of leukocytes in the sub-epithelial connective tissue. These cells are in about the same proportions as found in the larger bronchi. The blood vessels do not appear unusual. The lumina in many places are filled to a varying degree with rather dense mucoid material containing many lymphoid cells, plasma cells, and eosinophiles in about equal proportions. There is very little crystalline material seen.

Why did this woman go into status asthmaticus which resisted all treatment and led to death within a week? The exciting cause appeared to be an acute upper respiratory infection which produced a marked increase in the severity of her asthma. It is well known that infections of this type, popularly called colds, are the *bête noire* of numerous asthmatics, who may be quite comfortable in the intervals between these bouts of infection. The general population entertains these disorders in such large numbers, especially during the colder months of the year, that probably no striking decrease in their incidence can be brought about until a form of preventive vaccination, practicable on a large scale, can be developed.

Would altered treatment have resulted in her recovery? Undoubtedly the amount of epinephrine administered was very large—about 2½ oz. within five days. May not this have caused an exhaustion of the glycogen reserve of the body, where almost no food was consumed? Epinephrine, particularly in large amounts, may have unfavorable side effects. Doses as high as 1 c.c. which were given to her for a time, may actually be harmful and should seldom be used save in acute emergencies. From 0.2 to 0.4 c.c. is probably best for the average attack, repeated in 20 minutes or as often as may be necessary. The action of epinephrine is rapid but not sustained, hence the rationale of frequent doses which are not too large. In asthmatics who have become refractory to subcutaneous injections, intravenous epinephrine may give startling relief. Inasmuch as powerful effects may follow intravenous injections the initial dose must be very small. I have seen an attack of asthma broken in an epinephrine refractory patient by as little as 0.1 c.c. of 1–10,000 epinephrine intravenously.

Did the administration of morphine contribute toward this patient's death? She received within five days 14 hypodermic injections totaling 2⅝ grains. Not many physicians have seen asthma patients die following morphine administration, and case reports in the literature are uncommon. The statement is not infrequently made that morphine is dangerous in asthma and had better be withheld, but actual evidence bearing upon its action and results is scanty. Cohen and Rudolph [1] report that they have seen five patients with acute asthma in whom death followed within a few hours after morphine administration, and

FIG. 2. Small bronchus (low power and high power). Mucous plug filling lumen. Slight inflammatory reaction. No change in basement membrane.

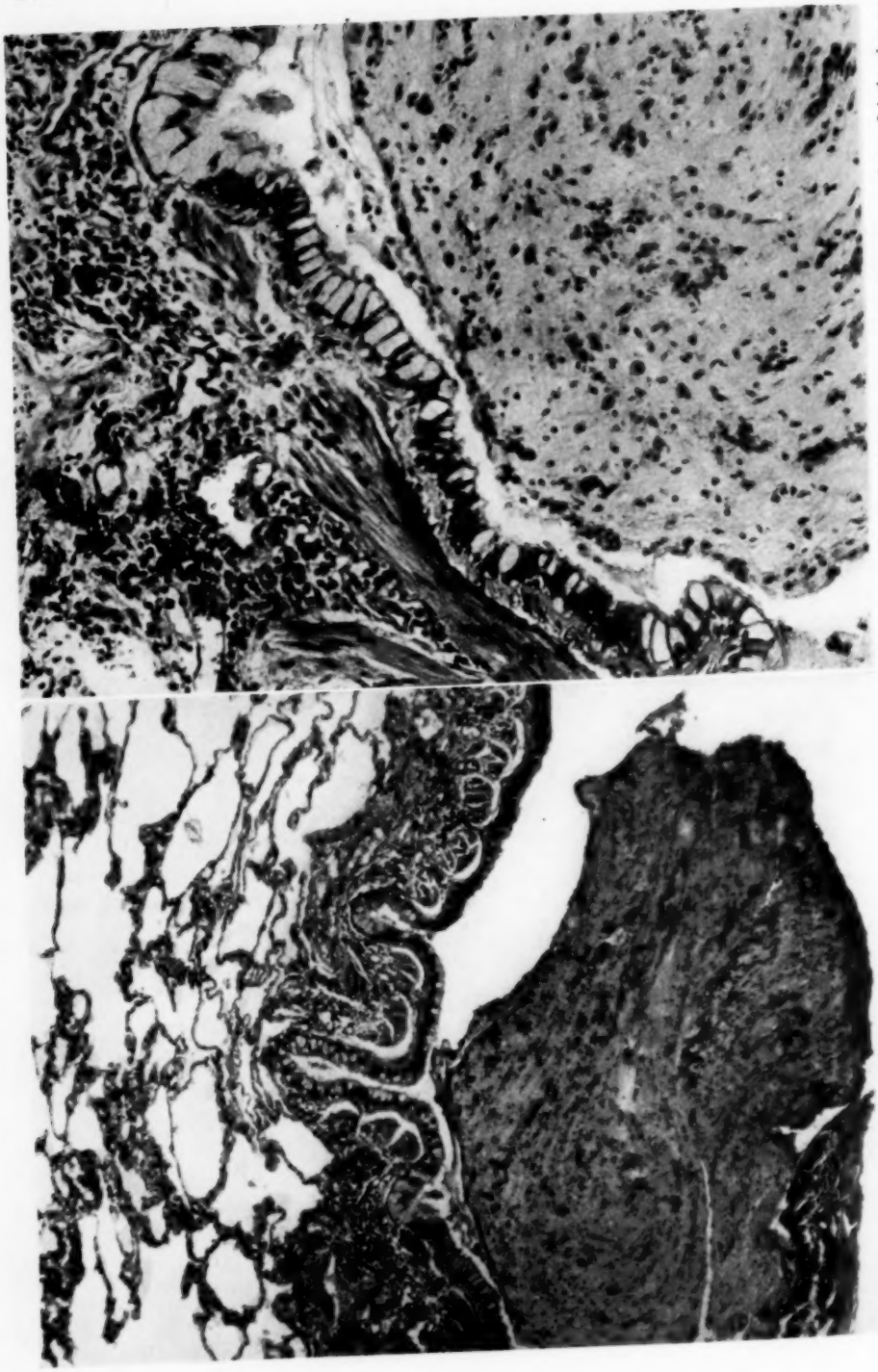

FIG. 3. Small bronchus (low power and high power). Mucous plug. Prominent goblet cells. Slight inflammatory reaction. Little change in basement membrane.

one case of death after codeine. The symptoms of asthma increased following morphine and the patients died respiratory deaths resembling strangulation. In two autopsied cases the entire bronchial tree was filled with a tenacious mucous exudate. The authors believe that:

1. Morphine depresses the respiratory center and makes respiration more shallow.

2. Abolition of the cough reflex makes it more difficult to expel mucous plugs.

3. Opiates may cause a hive reaction in the bronchial tree.

Jackson [2] states that morphine and other opium derivatives are able to produce bronchospasm by direct action upon the bronchial muscles, independently of the innervation, and that such a spasm is lasting and difficult to relieve by drugs with an opposing action such as epinephrine which stimulates the bronchodilator nerve endings. He raises the question as to the existence of two separate and distinct forms of bronchial asthma, the one of nervous, the other of muscular origin. Feinberg [3] considers morphine idiosyncrasy rather frequent among asthmatics and that a fatality may be hastened or brought on by its use. Sollmann [4] states that therapeutic doses of morphine produce slight bronchial relaxation whereas large doses cause marked constriction. "The relaxation may play a part in the relief of bronchial spasm (asthma); while the constriction may contribute to the asphyxia of toxic doses. The effects are peripheral for they occur on excised bronchial muscle." "The constrictor action is not antagonized by atropine and must, therefore, be on the muscle or myoneural junction." "Unless there is nausea the secretion of mucus appears diminished. This may be explained largely by the suppression of cough, permitting a longer sojourn of the mucus in the bronchi, with consequent removal of its water by absorption and drying; but there may also be a central depression." Personally I consider morphine a dangerous drug in asthma.

Would bronchoscopy have helped this patient? The finding of large amounts of tenacious mucus in the bronchial tubes and the knowledge that this is a common condition in severe asthma suggest that mechanical removal of the exudate would be exceedingly useful. The technical difficulties and possible danger of bronchoscopy in a seriously ill patient must be considered, but in some instances it will probably prove to be a life saving procedure.

Recently the inhalation of helium and oxygen has been suggested for the treatment of severe or intractable asthma. A mixture of oxygen 20 per cent and helium 80 per cent has one-third the density of atmospheric air and appears to enter narrowed air passages with much greater ease. Barach [5, 6] and Maytum et al.[7] have had some very favorable experiences. In severe asthma where the patients had become refractory to epinephrine, the relief of the paroxysm was accompanied by a return to normal epinephrine sensitiveness. With five patients in status asthmaticus Barach believes that lives were saved. Cylinders containing helium and oxygen in proper percentages are now on the market, and the inhalation of this mixture gives promise of being a very useful therapeutic agent, deserving of further clinical trial.

The pathological changes noted in this patient have been described by other observers. Emphysema, large amounts of thick tenacious mucus in the bronchial tree, infolding of the epithelial lining, fibrosis, prominence of goblet cells and

FIG. 3. Small bronchus (low power and high power). Mucous plug. Prominent goblet cells. Slight inflammatory reaction. Little change in basement membrane.

mucous glands, thickening and hyaline degeneration of the basement membrane, infiltration of the tissues with eosinophiles, all are well known findings. Others have described in addition increased thickness of the walls of the bronchi, hypertrophy of the muscle layers, myositis of the bronchial muscles and adhesive pleuritis. Hueber and Koessler [8] in their classical study of the pathology of bronchial asthma made very careful measurements of the bronchial tubes and came to the conclusion that the actual thickness of the walls of the bronchi and bronchioli of more than 0.2 mm. outside diameter is definitely increased.

Does a combination of the above described tissue changes indicate a characteristic pathology for bronchial asthma? Walzer [9] has well summarized the position of those who take a negative stand. He states that there is no one significant abnormality present in every case of asthma, nor are there any findings not met with in some other respiratory disturbance. He believes that the common secondary bronchitis and emphysema can cause increased thickness of the muscle layer and can produce most of the other changes. On the other hand Michael and Rowe [10] and Alexander [11] have stated that a pathological picture characteristic of bronchial asthma does exist. Hueber and Koessler [8] believed that the simultaneous occurrence of eosinophilia in the blood, sputum, and tissues does not occur in any other condition which could be confused with bronchial asthma.

Summary

A case of status asthmaticus is reported. Death appeared to be due to cardiac and general exhaustion. The rôle of the administration of large amounts of epinephrine and of morphine is discussed. Bronchoscopy is recommended in selected cases. The inhalation of helium and oxygen is considered. The pathological findings are similar to those reported in other patients who have died in acute asthma.

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EDITORIAL

THE PHYSIOLOGIC SIGNIFICANCE OF SWEATING

Human sweat glands, which according to Krause number about 2,380,000, are distributed over the entire surface of the body. Those in the axillary and inguinal regions are larger and of slightly different construction than are those situated elsewhere. The number in a specific region is greatest in the palms of the hands and the soles of the feet, next greatest in the forehead and least on the trunk and extremities. Kuno has reported that the extremities of Japanese, which are subjected to much exposure, contain a greater number of sweat glands than do the extremities of other races whose extremities are not exposed.

Sweating induced by heating the body occurs as a reflex mediated through the central nervous system and the sympathetic nerve fibers which supply the sweat glands. Langley, who first accurately described the secretory nerve fibers of animals, showed that they were part of the thoracicolumbar or sympathetic division of the autonomic nervous system. He demonstrated that sympathetic nerves contained fibers which control vasomotor reactions and sweating. If the vasomotor fibers were completely removed, sweating could not be demonstrated. Later, he showed by operation on cats that the nerve fibers concerned with sweating corresponded to the segmental distribution of the sympathetic nerves in the spinal nerves. He showed further that the area of skin supplied by the gray rami of each ganglion corresponded largely with the area of skin supplied by the homologous posterior root fibers.

Langley's observations on cats are applicable to man, as recent studies following bilateral cervicothoracic ganglionectomy, bilateral lumbar ganglionectomy and bilateral ventral rhizotomy have confirmed this segmental distribution of the sympathetic nerve fibers to the sweat glands. As a result of these studies it is possible to determine by tests of sweating what part of the sympathetic nervous system has been interrupted or removed.

There has been much controversy relative to the centers which control sweating. Evidence has been advanced by various investigators that sweat centers are situated in the cerebral cortex, the hypothalamic regions, the medulla oblongata and the spinal cord.

From a study of lesions of the spinal cord which affected soldiers, André-Thomas concluded that spinal centers for the innervation of the sweat glands of the head, neck, upper extremities and upper portion of the thorax, were situated between the eighth cervical and the sixth thoracic segments, and that those for the innervation of the sweat glands of the lower part of the trunk and extremities were situated between the sixth thoracic and upper lumbar segments. Head and Riddoch have shown that sweating which ceases temporarily after removal of the impulses from higher centers by

complete transection of the spinal cord not only returns eventually but that it becomes excessive.

Since sweating may be produced by mental effort, Kuno suggested that there might be a cortical center, and in confirmation of this, Guttmann reported that sweating occurred in response to electric stimulation of the cerebral cortex. However, Kuntz suggested that sweating induced by stimulation of the cortex might be produced by secondary impulses to the autonomic center in the hypothalamus. Cushing's studies on man have demonstrated that excessive sweating can be produced by injection of solutions of posterior pituitary, or pilocarpine into the cerebral ventricles. Since sweating is a part of the mechanism for reducing body temperature, it is probable that the center which controls it is situated in the hypothalamic region where the center for the regulation of the body temperature apparently is situated.

The most commonly used methods for determining sweating are the starch-iodine method and the cobaltous chloride method. In both of these tests the estimation of the degree of sweating depends on the change in the color of the material applied to the skin. In the starch-iodine test, when the skin is dry, the powder remains white; with the presence of sweat the color of the powder becomes deep blue-black. In the cobaltous chloride method, when the skin is dry the area to which the solution has been applied is deep blue in color but turns red on the appearance of sweat.

Sweating, which is a normal physiologic response, varies greatly among different individuals and under varying conditions. The reactions of the excretion of sweat are very sensitive to psychogenic factors, as is seen by the response to pain, gastrointestinal cramp, anxiety, joy, and the administration of nicotine. It is said that, in general, obese people, those who eat excessively, and those who have hyperthyroidism sweat excessively. Sweating is also increased in some cases of hemiplegia, herpes zoster, tuberculosis, hyperpituitarism, in most fevers, and in vasomotor disturbances such as Raynaud's disease. However, little clinical significance can be given to the presence of increased perspiration in any of these conditions. An example of marked increase in local sweating is that which affects the extremities without evidence of peripheral vascular disease. In some cases the hyperhidrosis in the hands and feet is so marked that it produces maceration of the skin and is disabling to a large degree. Adson, Craig, and Brown were of the opinion that this condition is a dysfunction of the sympathetic nervous system, which originates in the higher cerebral centers.

Diminution of sweat may occur in cases of poliomyelitis, multiple sclerosis, syringomyelia, myelitis, tumor of the spinal cord, and orthostatic hypotension. Since orthostatic hypotension is a disease which affects the vasomotor nerves and also the fibers that control sweating, the anhidrosis which occurs in orthostatic hypotension is of definite clinical importance. It is one of the characteristic abnormalities of the syndrome. Chew, Allen and Barker have reported anhidrosis to be present in 17 out of 21 cases. This lack of sweating varies in extent of distribution more or less with the

severity of the orthostatic hypotension. Anhidrosis also may occur as a result of degeneration of the sweat glands. Fog reported a case in which it followed a long standing febrile illness and biopsy of skin revealed that only about half of the sweat glands were present while the other half had undergone degeneration. A few cases in which generalized anhidrosis was due to congenital and general developmental anomaly of the skin have been reported.

Following the advent of surgical procedures on the sympathetic nervous system, it was found that anhidrosis produced by the interruption of the sympathetic pathways to a given cutaneous area is permanent. This provided a method for determining the distribution of the sympathetic nerve fibers to the sweat glands. Since hyperhidrosis was presumably the result of dysfunction of the sympathetic nervous system, sympathetic ganglionectomy was performed for the relief of this condition. The first two surgical interruptions of the sympathetic pathways for hyperhidrosis were made in 1921 by Kotzareff and in 1928 by Braeucker. In 1932 and 1934 Adson, Craig and Brown reported six cases of essential hyperhidrosis in which sympathetic ganglionectomy produced permanent relief. White has treated one patient who had hyperhidrosis, by paravertebral injection of alcohol into the upper thoracic ganglions; the sweating was definitely subnormal at the end of a year.

Although a great amount of investigative work has been done and considerable information has been obtained concerning the distribution of the sympathetic fibers to the sweat glands, the situation of sweat centers and the physiology of sweating in man, the clinical use of this knowledge is limited. According to Brown, the response of the secretion of sweat to a high environmental temperature determines the presence or absence of generalized or localized forms of anhidrosis, hypohidrosis or hyperhidrosis, and sweating tests will demonstrate whether complete denervation of the sympathetic fibers to a given area is present after sympathectomy. Repetition of the sweating tests at later intervals determines whether regeneration of nerve fibers has occurred. Clinically, anhidrosis is an important characteristic abnormality of orthostatic hypotension and surgical interruption of the vasomotor pathways will produce permanent relief in cases of hyperhidrosis.

G. M. R.

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REVIEWS

The Comparative Anatomy of the Nervous System of Vertebrates Including Man. By C. U. Ariens Kappers, M.D., the late G. Carl Huber, M.D., and Elizabeth Caroline Crosby, Ph.D. 2 volumes, 1845 pages. The Macmillan Co., New York City. 1936. Price, $16.00 per set.

The names of the authors of this important work are adequate guarantee of ability to handle an admittedly difficult subject. Started over ten years ago as a translation of Kappers' German text on the same subject, it soon outgrew the status of a translation and blossomed as a full fledged new work based upon the combined studies of both the senior and junior authors with such additions from other sources as seemed requisite to cover the broad scope of the work.

It may be stated at the outset that this book is not for the general practitioner of medicine or for those not familiar with neuro-anatomical structure and the technic of its investigation and presentation. But as a reference work, of which more will be said later, and for those concerned in neuro-anatomy and its application, it is a gold mine of information.

The work consists of two volumes of about 850 pages each. In spite of its size it is almost literally a glorified abstract of the subject matter covered, rather than an exhaustive discussion of any of the multiple subdivisions into which it divides itself. This is necessarily so because of the breadth of the subject itself.

The first volume discusses the phylogenetic development of the neurone, the spinal cord, the medulla oblongata in its broad sense, including the pons and the cerebellum. The structural significance of the spinal cord of each Class is discussed beginning with Amphioxus and ending with man. The same phylogenetic sequence is observed in describing the medulla oblongata, but here the subject is discussed in functional systems which are traced through the various Classes. Taste and tactile sensibility are first described, followed by the lateral line and vestibulo-cochlear afferent systems each being carried through the ascending forms of the vertebrate filum. The efferent motor system is similarly treated, including those motor centers resident in the midbrain. The organization of the reticular formation is then discussed. Under this head an unusual definition of the "final common path" is presented with a completely erroneous reference to Sherrington (1906) as the basis of the definition. The correlative function of these reticular centers is clearly demonstrated, but their acceptance as a final common pathway in the original sense of Sherrington is much to be doubted. An excellent discussion of the cerebellum concludes this volume.

Volume II treats of the midbrain and diencephalon as a unit to which about one-fourth of the volume is dedicated. The remaining three-fourths is devoted to the telencephalon. The analysis of the telencephalon is divided into two parts. The first takes up the non-mammalian forms, describing them in serial order up to the mammal. The latter is also included in this grouping except for the nonolfactory cortex. This subject is reserved for a special chapter in which it is treated in considerable detail. The discussion of the fundamental structure of the forebrain as determined by embryological evidence is regrettably lacking in completeness in that it does not include Kingsbury's (1920; 1922) interpretation of this process, particularly so since this author's findings are at variance with those favored in this book, though nonethe-less have been widely accepted elsewhere. A somewhat similar criticism may be made regarding the otherwise splendid discussion of the cerebral cortex in which the illuminating recent findings from the laboratories of Yale are conspicuous by their absence. This is explainable on the basis of the lapse of time since the inception of the work now under review though the omission seems hardly to be justified on this basis.

Each chapter of the book contains a resumé of the subject matter treated of in the chapter. This is arranged under subtitles indicative of the Classes under consideration and is an important and valuable feature of the book. The chapter ends with a bibliography pertaining to the chapter and arranged under subtitles like that of the resumé preceding it. Thus the seekers of bibliography in the lateral line system of Plagiostomes, or a like subject treated of in this book can in a moment locate the object of his search. These subject classification references consume in all about 250 pages and constitute in themselves a justification for the publication of the work.

Woven throughout the text are examples of the thesis of neurobiotaxis so closely associated with the name of the senior author, on the basis of which apparently disharmonious anatomical conditions of different species are harmonized and their significance interpreted.

The seven hundred plus illustrations adequately cover the text but the appearance of many of them is marred by indifferent labeling and the almost complete lack of descriptive technic in the legends limits their intelligent interpretation to those who are completely familiar with neuro-histological technic. This is a pity. A compensation exists, however, in the profusion of illustrations which the authors and publisher have managed to crowd into this work and still hold its publishing price at an astonishingly low figure. This is something for which an appreciative public will undoubtedly give thanks.

These volumes fill a want which has long existed in the English language and will remain as a worthy monument to the industry and genius of those who have produced them, one of whom, Dr. G. Carl Huber, unfortunately did not live to witness this climax to a busy and fruitful career.

C. L. D.

Recent Advances in Diseases of Children. By WILFRED J. PEARSON, D.S.O., M.C., D.M., F.R.C.P., and W. G. WYLLIE, M.D., F.R.C.P. 566 pages; 14.5 × 20.5 cm. Third Edition. P. Blakiston's Son and Co. Inc., Philadelphia, Pennsylvania. 1935. Price, $5.00.

The title "Recent Advances in Diseases of Children" does not correctly state the subject matter of this edition. In reality an attempt has been made to offer the general practitioner brief accounts of the illnesses of the young in a manner in which they are met in every day practice. The authors are concerned with the subjects primarily from a clinical aspect; important scientific data are mentioned if they are an aid clinically.

Certainly one of the assets of this book is its excellent organization which will make it helpful to the general practitioner. One is also impressed, however, by the lack of scientific discussion and of adequate references.

W. M. S.

The Principles of Bacteriology and Immunology. By W. W. C. TOPLEY, M.A., M.Sc., F.R.C.P., F.R.S., Professor of Bacteriology and Immunology, University of London, and G. S. WILSON, M.D., F.R.C.P., D.P.H., Professor of Bacteriology as Applied to Hygiene, University of London, London School of Hygiene and Tropical Medicine. Second Edition. 1645 pages; 18.5 × 25 cm. William Wood and Co., Baltimore. 1936. Price, $12.00.

The years that have passed since the publication of the first edition of this book have been years of renewed activity in research in the field of bacteriology and immunology. This has made necessary no inconsiderable revision of the text. A number of chapters have been rewritten, many have had much new material added, and hardly one has been left without partial revision. Several new chapters have been

included. All of this has been accomplished without greatly enlarging the book by a discreet omission of some of the older work and by a judicious selection from the newer. Nevertheless, its publication in a single volume in response to former criticisms would seem to make for inconvenience in reading. The second edition will undoubtedly maintain the same position as the first in the forefront of texts on the subject.

F. W. H.

Chemical Procedures for Clinical Laboratories. By MARJORIE R. MATTICE, A.B., Sc.M. 520 pages; 16 × 24 cm. Lea and Febiger, Philadelphia, Pa. 1936. Price, $6.50.

This is a comprehensive manual for chemical clinical laboratories. The author has included methods for the determination of the various constituents of blood, urine, feces, cerebro-spinal fluid and other body fluids. The chapter dealing with the chemical treatment of transudates and exudates is to be commended. The book should be valuable to those laboratories inexperienced in extensive work of this nature for the author has incorporated precautions and helpful changes in many determinations and has included only those methods which she has found satisfactory in her own laboratory. In other laboratories the book will be acceptable only in part since many of these methods will be neither suitable nor sufficiently recent for their use.

E. M. R.

Cancer Committee Studies. California Medical Association. 123 pages. J. W. Stacey, Inc., San Francisco, California. 1936. Price, $.75.

The book is paper bound and of small portfolio, with 123 pages. It contains the report of a cancer commission created by the House of Delegates of the California Medical Association in 1931. This commission appointed sub-committees to report on all phases of cancer therapy and in all specialties. The book is a timely one and should be read by every person interested in the cancer problem.

The first chapter is on Radiology. The Radiological Committee treats the question of "Radiology in the Treatment of Cancer," in a very safe and conservative manner. Following this, each special subject is reported upon by its own committee.

The great value of this book lies in the fact that it is not based on the experience of one man, nor one institution. "The Commission has made what it believes to be the first organized attempt to set forth the opinion of the medical profession rather than that of any one individual or clinic, or even one specialty." The purpose of the study is "to develop a better agreement in the profession and a wider diffusion of knowledge of the diagnosis and adequate treatment of early cancer." This aim has been closely adhered to and the book contains much valuable knowledge carefully compiled. The most up-to-date opinions about symptoms, onset, methods of diagnosis, treatment of early cancer, etc., are set forth, and where there is a controversy of opinion, especially as to treatment, both methods are given and the reasons for them stated. This book is a valuable adjunct to any physician's library.

G. E. W.

COLLEGE NEWS NOTES

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Grateful acknowledgment is made of the receipt of the following donations to the College Library of publications by members:

Books

Dr. Russell L. Cecil, Fellow, New York, N. Y., "Diagnosis and Treatment of Arthritis";

Dr. Henry A. Christian, Fellow, Boston, Mass., two autographed books, "The Diagnosis and Treatment of Diseases of the Heart" and "Medical Papers," the latter being a volume containing contributions dedicated to Dr. Christian;

Dr. E. B. Krumbhaar, Fellow, Philadelphia, Pa., an autographed copy, "Clio Medica. XIX. Pathology";

Dr. Edward C. Mason, Fellow, Oklahoma City, Okla., an autographed book "Why We Do It";

Dr. William D. Nimeh, Fellow, Mexico City, D. F., a book of poems by Dr. Nimeh.

Reprints

Dr. Dean B. Cole, Fellow, Richmond, Va., three reprints—"The Treatment of Pulmonary Tuberculosis" (with Walter L. Nalls, M.D.); "Ambulatory Pneumothorax" (with Edgar C. Harper, M. D.); "Therapeutic Use of Iodized Oil in Pulmonary Disease" (with Edgar C. Harper, M.D.);

Dr. Lewis B. Flinn, Fellow, Wilmington, Del., one reprint—"Preliminary Observations on the Clinical Use of Zinc-Protamine-Insulin in Out-Patients";

Dr. Cecil M. Jack, Fellow, Decatur, Ill., one reprint—"Some Unusual Features of Lung Cancer";

Dr. Hubert C. King, Fellow, Lakewood, Ohio, one reprint—"Prognosis in Coronary Heart Disease and After Coronary Occlusion";

Dr. Sinclair Luton, Fellow, St. Louis, Mo., one reprint—"Clinical Use of Digitalis: Variables Encountered";

Dr. Theodore H. Morrison, Fellow, Baltimore, Md., one reprint—"Idiopathic Ulcerative Colitis with a Report of an Unusual Case";

Dr. Albert E. Russell, Fellow, Washington, D. C., one copy of the Second Annual Memorial Lecture, "Silicosis and Other Dust Diseases";

Dr. Louis J. Bailey, Associate, Detroit, Mich., one reprint—"Paralysis of the Third Cranial Nerve Due to Spontaneous Hemorrhage Within the Nerve in the Latter's Intracranial Course" (with E. S. Gurdjian, M.D.);

Dr. Samuel Morrison, Associate, Baltimore, Md., six reprints—"The Pharmacopeia and the Physician" (with Julius Friedenwald, M.D.); "The Treatment of a Lung Abscess Due to *Bacillus Coli* with a Lytic Filtrate" (with Raymond E. Gardner, Sc.D.); "The Elimination of Various Dyes From the Pavlov Pouch of Dogs" (with David L. Reeves, M.D. and Raymond E. Gardner, Sc.D.); "The History of the Development of the Stomach Tube With Some Notes on the Duodenal Tube" (with Julius Friedenwald, M.D.); "The Medical Treatment of Peptic Ulcer" (with Julius Friedenwald, M.D.); "Value, Indications, Limitations and Technic of Colonic Irrigation" (with Julius Friedenwald, M.D.);

Dr. William Kendrick Purks, Associate, Vicksburg, Miss., seven copies of reprint—"Total Thyroidectomy for Heart Disease";

Dr. William R. Wirth, Associate, New Orleans, La., one reprint—"The Significance of Cardiac Arrhythmias as Encountered in General Practice."

Miscellaneous

Dr. Robert E. Schlueter, Fellow, St. Louis, Mo., a photograph album containing photographs of the pilgrimage to William Beaumont's grave by the American College of Physicians during its 1937 Session in St. Louis;

Dr. John A. Shuman, Fellow, Los Angeles, Calif., two lectures on "Southern California Medicine, Indian to Spanish Inclusive";

Rev. Harvey K. Heebner, Editor, The Schwenkfeldian, Philadelphia, Pa., a copy of "A Memorial to Dr. James M. Anders" (Master);

Mr. M. R. Kneifl, Executive Secretary, Catholic Hospital Association, St. Louis, Mo., one copy, "Special Directory Number of *Hospital Progress*."

At the last annual meeting of the State Medical Association of West Virginia, the following members of the College were elected to office: Dr. Charles W. Waddell (Fellow), Fairmont, W. Va., President; Dr. Arthur A. Shawkey (Fellow), Charleston, W. Va., Second Vice President; Dr. T. M. Barber (Associate), Charleston, W. Va., Treasurer.

Commander Eben E. Smith (Fellow), Medical Corps, United States Navy, has relieved Commander Louis H. Roddis (Fellow), Medical Corps, United States Navy, as editor of the "United States Naval Medical Bulletin" and as secretary of the Postgraduate Board.

During the Centennial Celebration, Davidson College, on June 8, conferred the honorary degree of Doctor of Science on Lieutenant Colonel James Stevens Simmons, Medical Corps, United States Army, now stationed at the Army Base, Boston, Mass., in recognition of his investigations on tropical diseases and preventive medicine.

At the eighty-seventh annual meeting of the Illinois State Medical Society, held in Peoria, May 18–20, Dr. Samuel E. Muson (Fellow and Governor for southern Illinois) was elected President-Elect of the Society.

Dr. Louis F. Bishop, Jr. (Fellow), New York, N. Y., recently attended, as a guest speaker, the West Virginia State Medical Association meeting in Clarksburg. He addressed the West Virginia Heart Association, May 24, on "Bundle Branch Block"; the Section on Internal Medicine, May 24, on "Fugitive Arrhythmias"; and the General Assembly, May 25, on "Prevention of Heart Disease."

Dr. Frank Burge (Fellow), Philadelphia, Pa., has been appointed Editor-in-Chief of "Diseases of the Chest," official journal of the American College of Chest Physicians. Dr. Burge is also an Associate Editor of Chest Diseases of the Cyclopedia of Medicine.

The American College of Chest Physicians is the new name adopted by the Federation of American Sanitaria, the change in name being adopted at Atlantic City during June.

Dr. Sinclair Luton (Fellow), St. Louis, Mo., presented a scientific exhibit on "Majors Errors Involved in the Use of Droppers for Liquid Digitalis Preparations" at the eightieth annual meeting of the Missouri State Medical Association during May.

Dr. Roy S. Leadingham (Fellow), Atlanta, Ga., presented a scientific exhibit and paper on "Rat Bite Fever" at the meeting of the American Society of Clinical Pathologists in Philadelphia, June 2–5.

The Fifth International Congress of Radiology will convene at the Palmer House, Chicago, September 13–17, 1937. It will be the first time that the world leaders in the medical and scientific development field of roentgen-ray and radium have met in America. The American Roentgen Society, the American College of Radiology, the Radiological Society of North America, and the American Radium Society will merge their meetings with the International Congress. "The Unity of Medicine" will be the theme of the entire Congress. Leaders in other branches of medicine will participate. More than 250 scientific papers will be read. They will be delivered in each lecturer's own language, but will be flashed on screens in English, German and French, as the papers are read.

The General Secretary of the Congress, Dr. Benjamin H. Orndoff (Fellow), is in charge of the headquarters at 2561 North Clark Street, Chicago. Dr. George E. Pfahler (Fellow), Philadelphia, is one of the honorary vice-presidents.

Dr. Nathan B. Van Etten (Fellow), New York, N. Y., Speaker of the House of Delegates of the American Medical Association, addressed the general assembly of the Minnesota State Medical Association at St. Paul, May 4, on "Medical Care for All Americans."

At the fifteenth annual meeting of the Philadelphia Heart Association, Dr. William D. Stroud (Fellow) was reëlected President, Dr. David Riesman (Fellow) was elected Vice President, Dr. Thomas M. McMillan (Fellow) was elected Secretary, and Dr. Edward B. Krumbhaar (Fellow) was elected a member of the Board of Governors.

Dr. William E. Robertson (Fellow) was inducted as President of the Philadelphia County Medical Society on July 1. Dr. Louis H. Clerf (Fellow) has been elected a Director.

Dr. E. J. G. Beardsley (Fellow), Philadelphia, Pa., was elected Secretary-Treasurer of the American Association of the History of Medicine at the last annual meeting of that organization at Atlantic City during May.

Dr. David Riesman (Fellow) received the honorary degree of Doctor of Laws from the University of Wisconsin at commencement June 21, 1937.

At the 131st Annual Meeting of the Medical Society of the State of New York, held at Rochester, N. Y., May 24, 25, 26, 1937, Dr. William A. Groat (Fellow), Syracuse, N. Y. was elected President-Elect of the Society.

Dr. Dwight O'Hara (Fellow), Professor of Preventive Medicine in Tufts College Medical School, has been appointed to the newly created position of vice-dean, to supervise clinical instruction in the third and fourth years.

Dr. Alfred Friedlander (Fellow), Professor of Medicine and Dean at the University of Cincinnati College of Medicine, has been appointed superintendent of the General Hospital to fill the vacancy caused by the death of Dr. Henry H. Langdon. Dr. Friedlander will continue his work in the medical school and act as superintendent only until a successor for the latter position can be found.

The American Association for the Study and Control of Rheumatic Diseases held its fourth annual meeting at Atlantic City under the presidency of Dr. Russell L. Cecil (Fellow), New York City. Dr. Cecil presented a paper on "The Necessity of Certain Criterion for the Diagnosis and Cure of Rheumatic Arthritis"; Dr. Bernard L. Wyatt (Fellow), Tucson, Ariz., gave a paper on "Experimentally Induced Jaundice"; Dr. Philip S. Hench (Fellow), Rochester, Minn., gave a paper on "Further Observations of the Effect of Jaundice on Atropic Arthritis and Fibrositis."

Dr. Lewellys F. Barker (Fellow), Baltimore, Md., discussed the "Progress of Endocrinology" at the twenty-first annual meeting of the Association for the Study of Internal Secretions at Atlantic City in June, under the presidency of Dr. F. M. Pottenger (Fellow), Los Angeles.

Dr. Paul D. White (Fellow), Boston, Mass., delivered the Alvarez Lecture on "The Differential Diagnosis of Cardiac and Gastro-Intestinal Disorders," before the fortieth annual meeting of the American Gastro-Enterological Association at Atlantic City in June, under the presidency of Dr. Chester M. Jones (Fellow), Boston, Mass.

Dr. Lewis A. Conner (Fellow), New York City, delivered the annual Henry Jackson Lecture of the New England Heart Association, April 30, on certain aspects of rheumatic fever and rheumatic heart disease.

Dr. Walter M. Boothby (Fellow), and Dr. William A. Plummer (Fellow), Rochester, Minn., addressed the annual meeting of the American Association for the Study of Goiter, held in Detroit, June 14–16, on "Interpretation of Basal Metabolic Rates in the Relatively Normal Individual."

Dr. George A. Harrop (Fellow), Baltimore, Md., has been appointed Director of Research on the staff of E. R. Squibb & Sons, according to a recent announcement. Dr. Harrop has been Assistant Professor of Medicine at Johns Hopkins University School of Medicine. E. R. Squibb & Sons are constructing a new research laboratory at New Brunswick, N. J. "Investigation along scientific lines will be carried on without necessary regard to its immediate practical outcome. It is also planned to undertake active clinical investigation with which to supplement and give orientation to the laboratory studies."

Dr. Horace W. Soper (Fellow), Dr. Frank D. Gorham (Fellow), and Dr. Lee Pettit Gay (Fellow), have been elected President, Vice President and Treasurer, respectively, of the recently formed Missouri Chapter of the National Society for the Advancement of Gastro-Enterology.

The following Fellows were selected to present graduate lectures in connection with the twenty-first annual course of medical lectures and clinics of the University of Washington from July 19–23: Dr. Anton J. Carlson, Professor of Physiology, University of Chicago; Dr. William S. Middleton, Professor of Medicine, University of Wisconsin Medical School, Madison; Dr. Hans Lisser, Clinical Professor of Medicine, University of California Medical School, San Francisco.

Dr. Mary Riggs Noble (Fellow), Philadelphia, Pa., was elected Treasurer of the American Medical Women's Association at its meeting in Atlantic City in June.

Dr. Jay A. Myers (Fellow), Minneapolis, Minn., was elected President of the National Tuberculosis Association at its annual meeting, June 2.

Dr. Ross M. Chapman (Fellow), Towson, Md., was installed as President of the American Psychiatric Association at its annual meeting in May.

Dr. Hugh B. Campbell (Fellow), Norwich, Conn., has been elected President-Elect of the Connecticut State Medical Association. Dr. Charles F. Turkington (Fellow), Litchfield, is President during the present year.

Dr. William R. Brooksher (Fellow), Fort Smith, Ark., has been elected Secretary of the Arkansas State Medical Association for the coming year.

OBITUARIES

DR. JOHN WYCKOFF

The sudden death of Dr. Wyckoff (Fellow) on June 1, 1937, at the age of 55 years, removed from this scene, in the prime of life and at the height of his professional career, one of the most widely beloved and respected members of the profession in New York City.

Born in Tindivanum, India, of Dutch Reform American Missionary parents, he spent two years in undergraduate study at Rutgers College, which institution later (1920) conferred upon him an honorary M.A. degree and still later made him a Trustee.

He was graduated in 1907 from the New York University and Bellevue Hospital Medical College and served his internship in Bellevue Hospital. After spending some time in various clinics in Germany he returned to New York to take up the practice of internal medicine. In 1914 he was married to Miss Elizabeth Crane Porter of Claverock, New York, who with his three children survives him.

Almost immediately after his return from study abroad he was made an Instructor in Medicine in the New York University school, in which he rose successively to the ranks of Clinical Professor, Associate Professor and finally (1932) Professor of Medicine. To his responsibilities as head of the department of medicine were added about the same time the onerous duties of Dean of the School.

He served successively as Adjunct Assistant Physician, Assistant Physician, and Physician and Director of the Third Medical Division of Bellevue Hospital, in which institution much of his professional life was spent.

One of the very first of the efforts directed toward the special care and rehabilitation of heart patients was the Bellevue out-patient cardiac clinic, established in 1911 by Dr. Hubert V. Guile. Two or three years later Dr. Wyckoff became associated with Dr. Guile in this clinic and, upon the

retirement of the latter in 1919, was made its head. Under his skillful guidance the clinic became one of the important agencies of the city for the training of physicians in heart diseases.

The special interest of Dr. Wyckoff in diseases of the heart was expressed in many ways. His writings were chiefly upon different aspects of this subject. For a long time he served as Chairman of the Heart Committee of the New York Tuberculosis and Health Association and of the Association of Cardiac Clinics. He was a Director, and later President, of the American Heart Association. In all of these capacities his work was characterized by the same unusual degree of energy, enthusiasm, vision and judgment that marked his services to the medical school and that played so important a part in the rapid development of that school. Indeed, it is given to few men to show such a record of successful achievement in so many fields of medicine as John Wyckoff could show.

His memberships included those in the New York County and State Medical Societies, American Medical Association, New York Academy of Medicine (Trustee, 1936), Association of American Physicians, American College of Physicians, Interurban Clinical Club, American Clinical and Climatological Association, American Association for the Advancement of Science, Association of American Medical Colleges (President, 1936).

But the mere listing of his accomplishments, appointments and connections would give a sadly inadequate picture of John Wyckoff the man. The things which won for him the deep affection and admiration of his fellow physicians and many friends were not so much his brilliant accomplishments as the personal qualities of modesty, honesty, courtesy, fair-mindedness and consideration for others. The world is much the poorer for the passing of John Wyckoff.

The above information has been supplied by Dr. Lewis A. Conner, F.A.C.P.

C. F. Tenney, M.D.,
Governor for Eastern New York, New York

DR. DOUGLAS BROWN

Dr. Douglas Brown (Fellow), Veterans' Administration Facility, Castle Point, N. Y., died June 6, 1937, at the age of sixty-seven.

Dr. Brown was born in New York City, later removing to Pottstown, Pa., where he attended the public schools. He attended the Sheffield Scientific School of Yale University, later entering Columbia University College of Physicians and Surgeons and graduating with the M.D. degree in 1894. In his early experience he was House Physician to the Fourth Division of the Bellevue Hospital, and Clinical Assistant in Neurology at the Vanderbilt Clinic, both of New York City. During 1908 and 1909 he served under General Gorgas at the Ancon Hospital, Panama. In 1910 he took postgraduate work at the Algemeines Krankenhaus, Vienna, in Pathology, Bac-

teriology, Internal Medicine, and Diagnosis. He entered the U. S. Veterans' Administration and served on various assignments over the United States, being classed as Internist-Expert in the Veterans' Administration.

Dr. Brown made numerous contributions to the literature. He was a member of the New York County Medical Society, the Medical Society of the State of New York, the American Medical Association, the Association of Military Surgeons, the Medical Veterans of the World War, the American Public Health Association, and had been a Fellow of the American College of Physicians since 1924.

DR. HAROLD BUNCE MYERS

Dr. Harold Bunce Myers (Fellow) of Portland, Oregon, died March 16, 1937, aged 50 years, of coronary thrombosis. At the time of his death he was Professor of Pharmacology and assistant dean of the Medical Department of the University of Oregon, having held both positions for more than 20 years. He took his bachelor's degree in the University of Wisconsin and graduated in medicine at Western Reserve University in 1911. He practiced a short time in Wisconsin and then went to New York where he was a member of the faculty at Bellevue Medical College, coming to Oregon in 1915 as head of the department of Pharmacology.

He had a keen interest in the welfare of medical students, and through contact with all applicants for admission to the school, had a closer acquaintance with the student body then others of the faculty: in many instances students received material aid through anonymous sources, because of his efforts. His activities in the university were many and his counsel was much appreciated.

His scientific contributions were numerous and research work in his department was wisely guided by him. He was a member of many scientific societies.

T. Homer Coffen, M.D., F.A.C.P.,
Governor for Oregon

DR. JOHN OSCAR ELROD

Dr. John Oscar Elrod (Fellow), Forsyth, Georgia; aged 59; died in a private hospital in Macon, Ga., on April 21, 1937. He was a native of Adairsville, Bartow County, and had practiced medicine in Monroe County and the adjoining counties for thirty-seven years. He attended the North Georgia Agricultural College and later graduated from the Atlanta College of Physicians and Surgeons, Atlanta (now Emory University School of Medicine), in 1901. He did post-graduate work in medicine and pediatrics at the New York Postgraduate Medical School in 1903.

Dr. Elrod served as major in the Medical Corps of the Georgia National Guard. He served on various committee assignments and in offices of the Medical Association of Georgia, being its president in 1924–25. For

a number of years and until the time of his death, he was a member of the State Board of Medical Examiners. Dr. Elrod was a member of the Monroe County Medical Society, Southern Medical Association, American College of Physicians and the American Medical Association. He was one of the most aggressive and loyal friends of organized medicine, also to his professional, civic and religious duties. Surviving him are his widow, two daughters, Mrs. Carlton Mobley, Atlanta; Miss Mildred Elrod, Forsyth; a brother, G. D. Elrod, Atlanta; his mother, Mrs. G. B. Elrod, Adairsville.

GLENVILLE GIDDINGS, M.D., F.A.C.P.,
Governor for Georgia

DR. DANIEL FRANCIS DALEY

Dr. Daniel Francis Daley (Fellow), Kingston, Pa., who had been in failing health for many months, died on April 24, 1937. He was born July 16, 1887, in Monmouthshire, Wales. His parents immigrated to this country when the future physician was an infant and his boyhood was spent in Luzerne, Pa., where he attended St. Mary's Academy. At an early age young Daley began to work in and about the coal mines and later through industry, loyalty and persistence in self-education, he was advanced to the responsible position of Chief Clerk of the Temple Coal Company.

Many youths would have considered that the far too early ending of formal education would prove a grievous handicap, but this lack acted as a stimulus in Daniel Daley's life and, without neglecting his duties to his employers, he established and carried out an admirable system of self-education at home. He completed a course of study far more extensive and intensive than many colleges require of their students and, having selected the profession of medicine as a career, he was accepted for entrance in the Jefferson Medical College of Philadelphia where he, in 1915, received his M.D. degree.

Dr. Daley served his internship in the Mercy Hospital, Wilkes-Barre, Pa., in which institution he later was to become pathologist.

Dr. Daley was an indefatigable student. He pursued his studies in the clinics of this country and abroad.

He was a member of the Philadelphia Pathological Society, the American Society of Clinical Pathologists and became a Fellow of the American College of Physicians in 1928.

Dr. Daley was a "good doctor." He was respected by fellow physicians and loved by his patients.

E. J. G. BEARDSLEY, M.D., F.A.C.P.,
Governor for eastern Pennsylvania

DR. EUGENE F. McCAMPBELL

Dr. Eugene F. McCampbell (Fellow), Columbus, Ohio, died May 8, 1937, of pneumonia at the age of fifty-five. Dr. McCampbell was born at

Marysville, Ohio, in 1883. He received the degree of Bachelor of Science in 1906 and the degree of Doctor of Philosophy in 1911 from the University of Chicago. His medical training was received at Rush Medical College, from which he graduated in 1912.

Dr. McCampbell was a teacher for a number of years previous to the time he studied medicine. He was Instructor in Bacteriology at the Ohio Medical University from 1903 to 1904; Assistant in Pathology at the University of Wisconsin during 1905 and 1906; Instructor in Bacteriology, 1906–08, Associate Professor of Bacteriology, 1908–10, Ohio State University College of Medicine. He served as Professor of Bacteriology, 1910–13, Professor of Preventive Medicine, 1913–27 and Dean, 1916–27, of the Ohio State University College of Medicine. He was Assistant in Pathology at the University of Chicago during the summers of 1908–11; Secretary and Executive Officer of the Ohio State Board of Health, 1912–16; Pathologist to the Columbus State Hospital, 1909–11. He had been a President of the Columbus Academy of Medicine and also a member of the Ohio State Medical Association, the American Medical Association, and had been a Fellow of the American College of Physicians since 1926. At the time of his death, he was a member of the Staffs of the Mount Carmel, Grant and White Cross Hospitals.

Dr. McCampbell was the author of a number of publications, including "Laboratory Methods for Study of Immunity" and co-author of "General Bacteriology."

DR. EARL B. SWEET

Dr. Earl B. Sweet, Fellow, died May 22, 1937, in Los Angeles following an operation on May 19. Dr. Sweet was born May 4, 1875, in Sloan, Iowa. He came to Los Angeles in 1887 and had his general education in the Los Angeles City Schools. He received his medical education at the University of Pennsylvania from which he was graduated in 1898. Dr. Sweet returned to Los Angeles to practise, early limiting his work to that division of effort which comes under Internal Medicine. He was a fine upstanding man, well known to his colleagues and with a wide and friendly acquaintanceship in the community. He was a charter member of the University Club. He belonged to his County, State and the American Medical Associations and the Southern California Medical Association. Though those who knew him realized that he was failing during the last few months, his cheeriness and hope remained with him until the last two weeks when he realized what he had to meet. In his death the community and the profession lost a fine man and member; they send their sympathy to his widow, who survives him.

EGERTON L. CRISPIN, M.D., F.A.C.P.,
Regent

MINUTES OF THE BOARD OF REGENTS

St. Louis, Mo.

April 18, 1937

A regular meeting of the Board of Regents was held at the Jefferson Hotel, St. Louis, April 18, 1937, with Dr. Ernest B. Bradley, President, presiding, Mr. E. R. Loveland acting as secretary, and with the following Regents present:

Ernest B. Bradley, *President*,
James H. Means, *President-Elect*,
O. H. Perry Pepper, *First Vice-President*,
David P. Barr, *Second Vice-President*,
Walter L. Bierring, *Third Vice-President*,
William Gerry Morgan, *Secretary-General*,
William D. Stroud, *Treasurer*,
William J. Kerr,
Roger I. Lee,
Sydney R. Miller,
George Morris Piersol,
G. Gill Richards,
Robert A. Cooke,
James B. Herrick,
Hugh J. Morgan,
James E. Paullin,
Egerton L. Crispin,
James Alex. Miller,
Francis M. Pottenger,
Charles H. Cocke,
Maurice C. Pincoffs,

and with Dr. Alfred Stengel as acting chairman of the Committee on Constitution and By-Laws.

Abstracted Minutes of the preceding meeting of the Board of Regents were read by the Executive Secretary, and, on motion, approved as read.

President Bradley announced that he had appointed a Committee to confer with the American College of Surgeons, his Committee consisting of the President, President-Elect and First Vice-President.

The Executive Secretary then read communications from Dr. E. W. Gehring, Governor of the College for Maine, dealing with the future policy of the College with respect to requirements of admission and the certification of physicians by the American Board of Internal Medicine; a communication from Dr. H. B. Logie, Executive Secretary of the National Conference on Nomenclature of Disease, thanking the College for its contribution to that organization's work; and a communication from Dr. James D. Bruce, Regent, expressing the opinion that the American College of Physicians should continue to admit to its membership those practicing specialties affiliated with Internal Medicine, and also expressing doubt as to the advisability, at the present time, of making certification by the American Board of Internal Medicine a prerequisite to membership.

President Bradley read a communication from Surgeon General Reynolds of the U. S. Army and a reply by Dr. James Alex. Miller, concerning the Harlow Brooks' memorial. Dr. Miller explained that a fund is being raised to be used by a committee in the memory of Dr. Brooks for the cause of medical education. He recommended that if the idea of cooperating appeals to the College, either approving the plan, or making a contribution, a general resolution to that effect could be adopted.

On motion by Dr. Roger I. Lee, seconded by Dr. James E. Paullin, and regularly adopted, it was

RESOLVED, that the Board of Regents appoint Dr. James Alex. Miller, a committee of one, to investigate the Harlow Brooks' Memorial Fund, and to report at some subsequent time to the Board of Regents for the appropriate action.

In subsequent discussion, it was pointed out that the College is much interested in the project, but not prepared to make a contribution to the Fund.

Dr. William Gerry Morgan, Secretary-General, was called upon for his report. He reported the deaths of the following members since the last meeting of the Board of Regents:

Master:		
Smithies, Frank	Chicago, Ill.	February 9, 1937
Fellows:		
Bartley, Elias H.	Brooklyn, N. Y.	January 12, 1937
Busby, James Leslie	Pasadena, Calif.	February 18, 1937
Crane, Augustus Warren	Kalamazoo, Mich.	February 20, 1937
Fales, Louis Henry	Livermore, Calif.	February 13, 1937
Frayser, Benjamin H.	Lexington, Ky.	March 5, 1937
Ghrist, David Garrison	Los Angeles, Calif.	February 3, 1937
Hodges, J. Allison	Richmond, Va.	December 15, 1936
Johnston, Collins H.	Grand Rapids, Mich.	December 29, 1936
Laubaugh, Ernest E.	Boise, Idaho	December 13, 1936
McKelvy, James P.	Pittsburgh, Pa.	January 28, 1937
Mink, Owen J.	M. C., U. S. Navy	October 21, 1936
Niemeyer, Charles Vincent	Union City, N. J.	January 11, 1937
Nisbet, Walter Olin	Charlotte, N. C.	January 18, 1937
Plummer, Henry S.	Rochester, Minn.	December 15, 1936
Redfern, Thomas C.	Winston-Salem, N. C.	October 16, 1936
Rich, William Lafayette	Salt Lake City, Utah	November 17, 1936
Stearns, William G.	Winnetka, Ill.	January 11, 1937
Waples, Frank A.	Houston, Tex.	March 3, 1937
Warren, Luther Fiske	Brooklyn, N. Y.	January 18, 1937
Wegge, William F.	Milwaukee, Wis.	November 20, 1936
White, William A.	Washington, D. C.	March 7, 1937
Associate:		
McCalla, Randolph L.	Boise, Idaho	October 10, 1936

Dr. Morgan further reported the following additional Life Members since the last meeting:

William Eugene Kendall	Oak Park, Ill.
Manfred Kraemer	Newark, N. J.
James W. Hunter, Jr.	Norfolk, Va.
Herbert B. Smith	Corning, N. Y.
Fresenius Van Nuys	Weston, Mass.
George M. Settle	Baltimore, Md.
Edward B. Vedder	Washington, D. C.
Robert A. Peers	Colfax, Calif.
Joseph D. Condit	Pasadena, Calif.
Charles W. Stone	Cleveland, Ohio
Samuel A. Vogel	Buffalo, N. Y.
Mills Sturtevant	New York, N. Y.
Russell M. Wilder	Rochester, Minn.
Cornelius Oliver Bailey	Los Angeles, Calif.

At this point, President Bradley called for resolutions on the deaths of certain of our former Officers and members. Resolutions had been presented both by Dr. Robert A. Cooke and Dr. James Alex. Miller on the late Dr. Luther Fiske Warren. Dr. Cooke presented the following resolution:

LUTHER FISKE WARREN

"The American College of Physicians records the death of Dr. Luther Fiske Warren on January 18, 1937, with sorrow and regret.

"Dr. Warren became a Fellow of this College in 1919, was chosen one of its Governors in 1931, and served as Regent from 1933 until his death. He was actively interested in the work of the College and served on several committees, especially the important Committee on Credentials.

"Dr. Warren prepared for his professional career at the University of Michigan, where he received his medical degree in 1909. His talent for teaching was recognized at once, and he served the Department of Medicine at Michigan until 1912, when he was invited to come to the Long Island Medical College, where he rose rapidly to become Professor of Internal Medicine, which position he filled with distinction from 1917 until his death.

"In addition to his work as a teacher, he filled an important place on the staff of many of the hospitals of Brooklyn and Long Island, and he brought wise counsel, clear vision and sound judgment to his many spheres of activity, and he was an outstanding influence in his community.

"A great understanding, kindly sympathy and complete devotion to the highest ideals of his profession commanded the affection and respect of those in this College with whom he came in contact, and in his death we have lost an honored colleague and a beloved friend. Therefore, be it

"RESOLVED, that the American College of Physicians records its sincerest and deepest sorrow in Dr. Luther Fiske Warren's death, its appreciation of his noteworthy services to his community and his profession, and, as a token of the esteem in which his memory will be held by the College, it is directed that this memorial be made a permanent record in the archives of the American College of Physicians and that a copy be sent to the members of Dr. Warren's family."

—ROBERT A. COOKE, M.D., F.A.C.P.

Dr. James Alex. Miller presented the following resolution:

LUTHER FISKE WARREN

"Dr. Luther Fiske Warren died at his home, 81 Pierrepont Street, Brooklyn, N. Y., on January 18, 1937. Long the head of the Medical Department in the old Long Island College Hospital and after its recharter in 1930 in the Long Island College of Medicine, Dr. Warren made his influence felt far beyond the confines of that institution.

"He was born in 1885 in Waterford, Mich. Working his way through school and college, he received his degree in Arts from the University of Michigan in 1907 and his M.D. from the same institution in 1909, attaining to membership in two honorary societies, Sigma Xi and Alpha Omega Alpha. For three years after graduation he remained at his Alma Mater serving as instructor in Clinical Microscopy and in Medicine.

"In 1912 he was called to Long Island as Assistant Professor of Medicine, being promoted to Associate Professor in 1915, and taking the Chair in Medicine in 1917, for a year as Acting Professor, and as full Professor in 1918. Besides directing the Medical Department of the College Hospital, Dr. Warren was Physician-in-Chief at St. Johns Hospital and Medical Director of the Brooklyn Home for Consumptives. He was Consulting Physician to the Lutheran, the Coney Island, the Methodist Episcopal Hospitals and the South Side Hospital at Bayshore.

"Dr. Warren was a brilliant clinician and teacher, and was endowed with vision and drive to an unusual degree. Among his many extramural activities should be listed the

Presidency of the Kings County Medical Society in 1930, Chairmanship of the Public Health Committee of the Brooklyn Chamber of Commerce, Directorship in the same organization, Directorship of the Brooklyn Council for Social Planning, and Chairmanship of the Brooklyn Health Council. He was a Trustee of the Polytechnic Institute and of the Packer Collegiate Institute. He was a Fellow of the New York Academy of Medicine, and a member of the American Medical Association, the American Heart Association, the National Tuberculosis Association, the Association for the Study of Internal Secretions, the American Society of Tropical Medicine and the American Society for the Advancement of Science.

"Dr. Warren was a Fellow of the American College of Physicians since June 19, 1919; he served as Governor for Eastern New York from 1931 to 1933 and as a Regent from 1933 to the date of his death. His counsel and advice have been of the greatest value to the Board of Regents in shaping the policies of the College. The Board of Regents very deeply mourn his loss and his absence from the Council Table will be very keenly felt; consequently, it is

"RESOLVED, that this Minute in the memory of Dr. Luther Fiske Warren be recorded in the records of the American College of Physicians in appreciation of his services to the College and to the medical profession and that a copy of this Minute be sent to members of his family.

—JAMES ALEX. MILLER, M.D., F.A.C.P."

On motion seconded and regularly adopted, it was

RESOLVED, that the above resolutions be adopted and spread upon the Minutes of this meeting.

Dr. William Gerry Morgan, as Secretary-General, then presented the following four resolutions on the late Dr. Harlow Brooks, Dr. Ernest E. Laubaugh, Dr. Frank Smithies and Dr. William Alanson White, which, by resolution unanimously adopted, were spread upon the Minutes of this meeting.

HARLOW BROOKS

"Whereas, it was the rare good fortune of the American College of Physicians to have had Doctor Harlow Brooks associated with it in membership throughout a period of twenty-three years, and to have enjoyed and profited by his active personal participation and interest in its scientific and other activities.

"His broad viewpoint and comprehension of medical problems, and the literary charm and forcefulness of his addresses and papers made his frequent and willing contributions to its programs of unexcelled value to the College. This value was greatly enhanced and enriched by the background of his personality in their presentation and his associations with its membership. Doctor Brooks was a man of great personal charm and friendliness, affable and lovable, a joy and an inspiration, and universally admired, esteemed, and beloved by his associates. The College not only shares in the loss to science and to humanity of this great and good man, but also suffers personal bereavement in the passing of a worthy and beloved personal friend.

"And whereas, it is fitting that the College record a testimonial of its appreciation of the life work and character of Doctor Brooks, of its happy personal relations with him over many years, and of its sorrow over his passing, together with an expression of its sympathy with the bereaved family.

"BE IT RESOLVED, that we express our deep sorrow for the loss of this true physician and wise counselor.

—WILLIAM GERRY MORGAN, M.D., F.A.C.P."

ERNEST E. LAUBAUGH

"Whereas, the American College of Physicians has lost, in the death of Dr. Laubaugh, one of its most devoted Fellows.

"Dr. Laubaugh died at Boise, Idaho, on December 13, 1936. He was born in Pennsylvania in 1887, and was graduated in medicine from the Medico-Chirurgical College in 1909. After interning at Mercy Hospital in Pittsburgh and later in the Philadelphia General Hospital, he became a member of the Faculty of his Alma Mater. In 1913 he resigned to accept the post of Bacteriologist with the Idaho State Board of Health, a position he held until 1917. At the time of his death, Dr. Laubaugh was a member of the Staff of St. Alphonsus and St. Luke's Hospitals in Boise.

"Dr. Laubaugh retired from the World War as Captain in the Army. He was a member of a good many medical and scientific societies and had made notable contributions to medical literature.

"And Whereas, Dr. Laubaugh was a former Governor of the College for the State of Idaho and took a keen interest in its welfare and upbuilding

"Be It Resolved, that the Regents express profound regret for the loss the College has sustained through the death of Dr. Laubaugh, and the sympathy which is felt for the bereaved family of the deceased.

—William Gerry Morgan, M.D., F.A.C.P."

Frank Smithies

"Whereas, Doctor Frank Smithies passed to his Eternal Home on February 9, 1937, at the age of 56 years. He was born in Elland, England, coming to the United States at the age of 5 years.

"Doctor Smithies was elected to Fellowship in the College in 1917, and throughout the subsequent years he was very active in the participation of its growth and development.

"Doctor Smithies gave unsparingly of his time and energies to the work of the College. To his foresight and directing influence does the College owe not merely its very existence, but the sane lines of its progress.

"Therefore Be It Resolved, that the American College of Physicians through its Board of Regents express the profound regrets and deep sorrow for the loss of this highly valuable and interested Master, who had served as Regent, Secretary-General and President.

—William Gerry Morgan, M.D., F.A.C.P."

William Alanson White

"Whereas, Dr. William Alanson White died on March 7, 1937, in Washington, D. C., in his 67th year.

"Dr. White was elected to Fellowship in 1923, and was keenly interested in the progress and welfare of the College. As Superintendent of St. Elizabeths Hospital at Washington, he had under his supervision more than six thousand insane patients and over one thousand employees, as well as a large staff of expert physicians. The responsibilities incident to directing such a large and complex institution rendered it impossible for him to attend all of the Annual Meetings of the College, which was a source of profound regret to him.

"Dr. White was a man of innate kindliness, always ready to extend a helping hand to all who sought his aid. He was universally admired and beloved by his immediate associates, the profession at large and by many in all walks of life.

"And Whereas, it is fitting that the College express its appreciation of the life work and character of Dr. White, of his influence for the betterment of his fellowmen, and of its sorrow at his death, together with an expression of its sympathy with the bereaved family.

"Therefore Be It Resolved, that we express our profound sorrow for the loss of this distinguished physician from our membership.

—William Gerry Morgan, M.D., F.A.C.P."

Dr. George Morris Piersol presented the following resolution on the late Dr. James M. Anders, which, upon motion unanimously adopted, was spread upon the Minutes of the meeting.

JAMES M. ANDERS

"It is with deep sorrow and regret that we record the death of our distinguished past-president (1922), Dr. James M. Anders, of bronchopneumonia on August 29, 1936.

"Dr. Anders was a native of Pennsylvania, born on July 22, 1854. After a careful preliminary education he was graduated from the Medical School of the University of Pennsylvania in 1877. His subsequent career proved him to be a worthy son of that celebrated Class which furnished so many outstanding men to the medical profession of this country. The year he graduated in medicine, Dr. Anders also received his Ph.D. His early interests centered about the biological and medical sciences. The original investigations which he conducted into certain plant functions earned for him recognition by the French Government, which made him an Officier de l'Instruction Publique et des Beaux Arts.

"Dr. Anders attained his greatest distinction, however, in his chosen field of Internal Medicine and Public Health, for which he prepared himself thoroughly by many years of active affiliation with a number of Philadelphia's leading hospitals.

"As a teacher, Dr. Anders exhibited exceptional ability. In 1889 he became associated with the Medico-Chirurgical College of Philadelphia. By 1893 he had been made Professor of the Theory and Practice of Medicine and Clinical Medicine in that institution—a position which he graced with distinction for twenty-five years.

"Dr. Anders' interest in public health and tuberculosis prevention led him to take an active part in civic affairs. From 1914 on he served as a member of the Board of Health of Philadelphia. He became a leading figure in many local, state and national health movements.

"One of Dr. Anders' outstanding achievements in medical education was the role he played in bringing about the merge of the Medico-Chirurgical School with the University of Pennsylvania, which resulted in the present Graduate School of Medicine at Pennsylvania. He took an active part in the development and direction of this institution, serving until his death as one of its managers, and, through his broad vision and enthusiasm, contributing in no small measure to its growth and success.

"Dr. Anders was a prolific, scholarly and popular author. In addition to innumerable original articles, he contributed to medical literature his large work on the "Theory and Practice of Medicine," which went through fourteen editions and later a text-book on "Medical Diagnosis." Not content with medical writings, Dr. Anders wooed the Muse of poetry, publishing in 1934 a delightful volume, entitled "Meditations in Verse."

"As a reward for his accomplishments in medicine, public health and education, Dr. Anders received numerous honorary degrees, was made a Chevalier of the Legion of Honor of France in 1923, and the same year had the distinction of being the first Fellow of this College to be made a Master.

"The crowded, varied, but fruitful career of Dr. Anders was marked by signal successes. As a doctor, teacher, author, educator and public spirited citizen, he has earned the gratitude of his chosen City of Philadelphia and left an indelible imprint upon the progress of American Medicine.

—GEORGE MORRIS PIERSOL, M.D., F.A.C.P."

Dr. Sydney R. Miller, Chairman of the Committee on Credentials, reported that his Committee had held two meetings—one on March 14, 1937, and one on April 18, 1937. At the meeting on March 14, the credentials of sixty-two candidates for Fellowship were examined. Of this number, the Committee recommended the rejection of four, deferment of thirteen for further material, time or investigation, and the election of forty-five. Of those recommended for election, thirty-nine were for advancement from Associateship and six for direct election. In one case, a candidate had served a five-year Associate term from 1931 to 1936, but because of critical illness was unable to qualify in the five-year period, and had been dropped. The Committee, however, credited his five-year Associate term and included his name among those for advancement now.

At the meeting of March 14, the Committee examined the credentials of eighty-seven candidates for Associateship, of which they recommended the rejection of ten, the deferment of six and the election of seventy-one.

At the meeting of the Committee on April 18, they considered the credentials of fifty-two candidates for Fellowship, of which they recommended forty-seven for election; one for election to Associateship, and four for deferment for further credentials.

At the meeting on April 18, they also considered fifty-seven candidates for Associateship, of which they recommended forty-seven for election, six for rejection and four for deferment.

The combined recommendations for election of the Committee on Credentials, as included in lists of names passed around for inspection by the Board of Regents, included ninety-two Fellows and one hundred and nineteen Associates.

Upon motion by Dr. Robert A. Cooke, seconded by Dr. Maurice C. Pincoffs, and regularly carried, it was

RESOLVED, that the following candidates shall be and are herewith elected to the respective class of Fellowship or Associateship as recommended.

Elected to Fellowship:

Name	City and State
1. Archambeault, Charles Pahl	M. C., U. S. Navy
2. Arkin, Aaron	Chicago, Ill.
3. Baehr, George	New York, N. Y.
4. Baer, Ridgely Waters	Frederic, Md.
5. Barry, Michael William	Omaha, Nebr.
6. Bergstrom, Victor William	Binghamton, N. Y.
7. Bernton, Harry Saul	Washington, D. C.
8. Bishop, F. Warner	New York, N. Y.
9. Boots, Ralph Henderson	New York, N. Y.
10. Brand, Alonzo Frederick	Fayetteville, N. Y.
11. Chapman, Edward Northrop	Colorado Springs, Colo.
12. Clark, Cyrus J.	Indianapolis, Ind.
13. Cole, Rufus	New York, N. Y.
14. Collins, Russell Johnson	East St. John, N. B., Can.
15. Cooke, William Clifford	San Diego, Calif.
16. Cooksey, Warren B.	Detroit, Mich.
17. Curran, Jean A.	Brooklyn, N. Y.
18. Dale, Grover Cleveland	Goldsboro, N. C.
19. Davies, Willard John	Rockville Centre, N. Y.
20. DeGraff, Arthur Christian	New York, N. Y.
21. de la Chapelle, Clarence E.	New York, N. Y.
22. Denny, Earl Rankin	Tulsa, Okla.
23. Du Bois, Eugene Floyd	New York, N. Y.
24. Duggan, LeRoy Bates	Houston, Tex.
25. Ecker, Lewis Charles	Washington, D. C.
26. Ensign, Dwight Chester	Detroit, Mich.
27. Fearon, Henry Dana	Brooklyn, N. Y.
28. Fischer, Carl Castle	Philadelphia, Pa.
29. Frissell, Lewis Fox	New York, N. Y.
30. Geyelin, H. Rawle	New York, N. Y.
31. Goldring, William	New York, N. Y.
32. Goodwin, George Munro	New York, N. Y.
33. Gray, George Albert	Sweetwater, Tex.
34. Haden, Russell Landram	Cleveland, Ohio

35. Harmeier, John Watson	Pittsburgh, Pa.
36. Henrichsen, Karl Johan	Chicago, Ill.
37. Hines, Edgar Alphonso, Jr.	Rochester, Minn.
38. Hofrichter, Cassius Howard	Seattle, Wash.
39. Hookey, John Arlington, Sr.	Detroit, Mich.
40. Huntington, Herbert Arthur	Los Angeles, Calif.
41. Hutton, Robert LeRoy	New York, N. Y.
42. James, Henry	New York, N. Y.
43. Jolliffe, Norman	New York, N. Y.
44. Kitzmiller, Karl Vivian	Cincinnati, Ohio
45. Knowles, George Milton	Hackensack, N. J.
46. Kovnat, Maurice	Staten Island, N. Y.
47. Krombein, Walter H.	Buffalo, N. Y.
48. Lamb, Albert Richard	New York, N. Y.
49. Lande, Herman	New York, N. Y.
50. Larimer, Robert Newell	Sioux City, Iowa
51. Leivy, Frank Edward	Philadelphia, Pa.
52. Leslie, George L.	Howell, Mich.
53. Lichty, John Max	Pittsburgh, Pa.
54. Lincoln, Asa Liggett	New York, N. Y.
55. Loeb, Robert Frederick	New York, N. Y.
56. Marvin, Horace Page	M. C., U. S. Army
57. McAlpin, Kenneth Rose	New York, N. Y.
58. McEwen, Currier	New York, N. Y.
59. Mendelson, Joseph A.	Tientsin, China
60. Miller, Aura James	Louisville, Ky.
61. Moon, Arthur Ernest	Temple, Tex.
62. Morgan, Philip Wilhelm	Emporia, Kan.
63. Muhl, Anita M.	San Diego, Calif.
64. Oppenheimer, Bernard Sutro	New York, N. Y.
65. Patterson, Henry Stuart	New York, N. Y.
66. Piness, George	Los Angeles, Calif.
67. Powell, Vernon Edwin	Atlanta, Ga.
68. Ralli, Elaine Pandia	New York, N. Y.
69. Reed, E. Burkett	Lincoln, Nebr.
70. Reinhard, Otto A. G.	Lincoln, Nebr.
71. Rousseau, James Parks	Winston-Salem, N. C.
72. Russell, Richard Olney	Birmingham, Ala.
73. Ryan, William Joseph	Pomona, N. Y.
74. Shearer, Leander H.	New York, N. Y.
75. Simons, Samuel Shirk	Lancaster, Pa.
76. Smith, Dudley Crofford	University, Va.
77. Speed, Henry Kirven	Sayre, Okla.
78. Stillman, Edgar	New York, N. Y.
79. Strong, George Frederic	Vancouver, B. C., Can.
80. Stygall, James Henry	Indianapolis, Ind.
81. Taylor, Kenneth	New York, N. Y.
82. Tidmarsh, Clarence Johnson	Montreal, Que., Can.
83. Trump, Frank	Ottawa, Kan.
84. Unger, Leon	Chicago, Ill.
85. Vogel, Karl	New York, N. Y.
86. Walker, Hastings Howland	Honolulu, T. H.
87. Weirauk, Herbert Vance	Columbus, Ohio
88. Wellman, Harvey Elijah	Providence, R. I.

89. West, Randolph	New York, N. Y.
90. Westcott, Franklin Howard	New York, N. Y.
91. White, Thomas Joseph	Jersey City, N. J.
92. Woodruff, Isaac Ogden	New York, N. Y.

Elected to Associateship:

Name	City and State
1. Adams, Walter Paul	Norfolk, Va.
2. Alexander, Harry Allison	Boulder, Colo.
3. Ashley, Claude Wilber	Bloomsburg, Pa.
4. Atkinson, Harold Cook	Macon, Ga.
5. Badger, Theodore Learnard	Boston, Mass.
6. Bayley, Robert Hebard	New Orleans, La.
7. Bell, Joseph Clark	Louisville, Ky.
8. Blitch, Clifford Gordon	M. C., U. S. Army
9. Block, Morris	New York, N. Y.
10. Bohner, Caryle Bernard	Indianapolis, Ind.
11. Brown, Marshall Stewart, Jr.	New York, N. Y.
12. Burger, Aaron L.	Brooklyn, N. Y.
13. Cadden, Anthony Vandril	Hopemont, W. Va.
14. Cannady, Edward Wyatt	East St. Louis, Ill.
15. Ceder, Elmer Theodore	U. S. Public Health Service
16. Chamberlain, Charles Thomson	Fort Smith, Ark.
17. Chilko, Alexander J.	New Rochelle, N. Y.
18. Cooper, Henry Lewis	Denver, Colo.
19. Culp, John Ewart	Ithaca, N. Y.
20. Dixson, Ira Milburn	Stockbridge, Mass.
21. Dozzi, Daniel Louis	Philadelphia, Pa.
22. Driscoll, Charles Dennis	Haddon Heights, N. J.
23. Dyrenforth, Lucien Young	Jacksonville, Fla.
24. Falisi, James Vincent	M. C., U. S. Army
25. Farrar, George Elbert, Jr.	Philadelphia, Pa.
26. Fatherree, Thomas Jefferson, Jr.	Rochester, Minn.
27. Findley, Thomas Palmer, Jr.	St. Louis, Mo.
28. Fink, Harold	Brooklyn, N. Y.
29. Finnigan, Francis Roman	St. Louis, Mo.
30. Foley, Maurice P.	Rochester, Minn.
31. Foster, Frank Pray	Rochester, Minn.
32. Fuendeling, Mervyn Julius	Twin Falls, Idaho
33. Gandara, Jose Nicolas	Ponce, P. R.
34. Glenn, Elmer Edward	Springfield, Mo.
35. Gosline, Harold Inman	Ossining, N. Y.
36. Goodrich, Murray Eugene	Toledo, Ohio
37. Greenhouse, Barnett	New Haven, Conn.
38. Gutman, Alexander B.	New York, N. Y.
39. Hall, Byron Ellsworth	Rochester, Minn.
40. Hammonds, Everett England	Birmingham, Mich.
41. Harris, Robert Miller	Miami, Fla.
42. Hart, Andrew DeJarnette, Jr.	Charlottesville, Va.
43. Hausheer, Walter C.	Staten Island, N. Y.
44. Hedley, Oswald F.	U. S. Public Health Service
45. Hemingway, Max William	Bend, Ore.
46. Hershenson, Morris A.	Pittsburgh, Pa.
47. Houck, George Hamilton	Los Angeles, Calif.

48. Hutton, John Evans	New York, N. Y.
49. Jacobs, Minard F.	Oklahoma City, Okla.
50. Johnson, Alf Cornelius	Great Falls, Mont.
51. Jukes, R. Franklin	Akron, Ohio
52. Kandel, Harry Milton	Savannah, Ga.
53. Katzman, Maurice	Denver, Colo.
54. Kendall, Charles Benjamin	M. C., U. S. Army
55. Kinney, James P.	Buffalo, N. Y.
56. Kneeland, Yale, Jr.	New York, N. Y.
57. Koons, Ruth Alice	Columbus, Ohio
58. Lake, Michael	New York, N. Y.
59. Langdon, Roy Luther	Philadelphia, Pa.
60. Lansbury, John	Philadelphia, Pa.
61. Ledbetter, Abbe Alzu	Houston, Tex.
62. Leser, Ralph Ulrich	Bloomington, Ind.
63. Lewis, William Hall, Jr.	New York, N. Y.
64. Lieberman, John F.	M. C., U. S. Army
65. Logie, Arthur J.	Jacksonville, Fla.
66. Madden, Lucius Emmett	Columbia, S. C.
67. Mahon, Hugh William	M. C., U. S. Army
68. Margulis, Aaron E.	Mount Morris, N. Y.
69. Martin, George Graydon	Buffalo, N. Y.
70. McCall, Marsh	New York, N. Y.
71. McGrath, Robert	New York, N. Y.
72. Monroe, Robert Thornhill	Brookline, Mass.
73. Morales, Luis M.	Santurce, P. R.
74. Morlock, Carl Grismore	Rochester, Minn.
75. Murphy, Robert Gordon	Providence, R. I.
76. Nichol, Arthur Dale	Cleveland, Ohio
77. Nicklas, John M.	Valhalla, N. Y.
78. Nickum, John Stanley	Bridgeport, Conn.
79. Noyes, Edward Allen	M. C., U. S. Army
80. Olson, Andrew Allen	Wichita, Kan.
81. Ormond, Alexander Pierce	Akron, Ohio
82. Paley, Samuel S.	New York, N. Y.
83. Parker, Robert Lawrence	Rochester, Minn.
84. Perakos, George	Philadelphia, Pa.
85. Persons, Elbert Lapsley	Durham, N. C.
86. Peters, John	Maywood, Ill.
87. Poole, Wallace L.	Johnson City, Tenn.
88. Prince, Homer Edward	Houston, Tex.
89. Redelings, Leslie Hall	San Diego, Calif.
90. Richards, Calvus Elton	Gallipolis, Ohio
91. Robb, George Porter	New York, N. Y.
92. Rudesill, Cecil Logan	Indianapolis, Ind.
93. Russman, Charles	Middletown, Conn.
94. Salkin, David	Hopemont, W. Va.
95. Sander, Oscar A.	Milwaukee, Wis.
96. Schwartz, Jacob	Brooklyn, N. Y.
97. Scovel, Frederick Gilman	New York, N. Y.
98. Sharkey, Thomas Palmer	Dayton, Ohio
99. Sharp, Ezra Abraham	Providence, R. I.
100. Solomon, Charles	Brooklyn, N. Y.
101. Solomon, Reuben A.	Indianapolis, Ind.

102. Sours, James W.	Peoria, Ill.
103. Sparks, Munroe Irving	Cleveland, Ohio
104. Steinberg, Israel	New York, N. Y.
105. Strickler, Cyrus Warren, Jr.	Atlanta, Ga.
106. Sugarman, Harold	Saskatoon, Sask., Can.
107. Torbett, John Walter, Jr.	Marlin, Tex.
108. Townsend, James Harvey	Boston, Mass.
109. Trapp, Carl Edward	Boston, Mass.
110. Ulmar, David	New York, N. Y.
111. Van Buren, Ebert	Atlanta, Ga.
112. Walker, George Leonard	Griffin, Ga.
113. Wallace, Robert Pulley	New York, N. Y.
114. Walsh, Edmund Michael	Omaha, Nebr.
115. Ward, Albert Gayden	Jackson, Miss.
116. Weinstein, Albert	Nashville, Tenn.
117. Weinstein, Joseph	Brooklyn, N. Y.
118. Wilder, Gordon Botkin	Anderson, Ind.
119. Woldman, Edward Elbert	Cleveland, Ohio

Dr. Sydney R. Miller, as Chairman of the Committee on Credentials, further reported that they recommend to the Board of Regents that the name of Dr. Fernando Ocaranza, of Mexico, D. F., be dropped from the Roster of Fellows, because he had failed to take up his election to Fellowship by the payment of the prescribed fees and dues in accordance with the By-Laws.

On motion by Dr. Sydney R. Miller, seconded by Dr. James E. Paullin, and regularly carried, it was

RESOLVED, that the name of Dr. Fernando Ocaranza, Mexico, D. F., be dropped from the Roster of Fellows because of failure to take up his election in accordance with the Constitution and By-Laws.

Dr. Sydney R. Miller, as Chairman of the Credentials Committee, presented the following resolution which had been unanimously adopted by his Committee at their meeting in Philadelphia on March 14:

RESOLVED, that reconsideration of the proposed amendments to the Constitution and By-Laws be gone into by the Board of Regents before being proposed at the Annual Session.

President Bradley explained that the members of the Credentials Committee have a very deep interest in the question of changes in the standards of admission anticipated by amendments proposed at the December, 1936, meeting of the Board, and felt particularly that the provision that certification should be a prerequisite for Associateship should be reconsidered; also the matter of "affiliated specialties."

On motion by Dr. Bierring, seconded by Dr. Means, and regularly carried, the resolution presented by the Committee on Credentials was adopted.

There followed open discussion concerning the amendments proposed to the Constitution and By-Laws at the Regents' meeting during December, 1936.

Dr. James Alex. Miller expressed regret that Dr. Jonathan C. Meakins, a member of the Committee on Constitution and By-Laws, was not present to join in the discussion. Dr. Miller said that he thought it premature to put the proposed amendments into effect, for the reason that the question of certification of internists has not yet been established on a firm footing. If the Credentials Committee continues as it has in the past to closely scrutinize the credentials of every candidate, and even to more carefully investigate their credentials, the College may proceed on its present basis, giving the American Board of Internal Medicine more time to get established. The College should at least preserve its independence of action, and in his opinion the Board might do well to withdraw both the proposed amendments until some later time.

Dr. Walter L. Bierring, Chairman of the American Board of Internal Medicine, dis-

cussed the proposed amendments adopted during December, 1936, and suggested that certification might more properly be made a prerequisite for Fellowship, rather than for Associateship. He reported that to that date eighty-six applicants had applied for the examinations of the Board, and prophesied that in three or four years the Board may be called upon to examine about two hundred candidates a year, which is about the same as the number of elections to Fellowship in the College.

In part, Dr. Bierring said, "The type of Fellows of the College would be such as had been certified as internists under the proposed newer regulations. It is difficult to formulate any kind of a plan that would include distinguished men who would not come under the head of certified internists, whom we would feel honored to have made Fellows of this College, whether they were in an allied field or not, and it seems to me they should be in, if they can qualify. But, the American College of Physicians is an association of internists, as we understand it, and we feel that we might approximate somewhat to the standards and ideals of the Royal College of England and Scotland, if an examination is one of the qualifications for election. It is true that these Colleges also elect to Fellowship obstetricians, pediatricians, neurologists and other allied branches of Internal Medicine, not surgical."

Chairman Bradley pointed out that at the present time the American College of Physicians is not for internists only, but for those engaged in internal medicine and allied specialties.

At this point, Dr. Alfred Stengel, Acting Chairman of the Committee on Constitution and By-Laws, was called upon to make a report.

After discussing various considerations that had been presented to the Committee, Dr. Stengel summed up his remarks by saying that "it was the recommendation that the Board of Regents withdraw from the proposed amendments altogether at this time, because they feel the action is premature."

Dr. Stengel pointed out that another proposal had been received by the Committee, namely, to make provision for the legalization of alternates for the members of the Board of Governors who may be unable to attend the Annual Meetings. The following amendment had been formulated by Dr. Jonathan C. Meakins, the Chairman of the Committee:

> "Any member of the Board of Governors unable to attend the Annual Session shall appoint as his alternate, with all the privileges of a Governor, a Master or Fellow of his district who will be in attendance at that Session. Upon presentation to the Chairman of the Board of Governors of a certificate of appointment, the alternate shall be recognized and act in the full capacity of Governor for the Session to which he has been appointed. The same alternate shall not be appointed for more than two consecutive years."

This amendment had not previously been presented to the Board of Regents for approval.

Dr. Stengel recommended that if the other recommendations for alterations in the Constitution and By-Laws are to be laid on the table for the present, it might be well to defer action also on the above proposal until another year.

On motion by Dr. Walter L. Bierring, seconded by Dr. Sydney R. Miller, it was

RESOLVED, that the Board of Regents, after thoroughly studying the situation, withdraw the proposed amendments to the Constitution and By-Laws as considered at the December, 1936, meeting of the Board and subsequently published in the "Annals of Internal Medicine"; and, further, any other amendments for action at the Annual Business Meeting during the current year.

In the discussion of the resolution, Dr. Maurice C. Pincoffs said in part, "These amendments have been read by all the members. That need not influence the Board in any way, but I think the motion before the house is something I favor, but I would like to present one point about it before we act, namely, there are a number of other solutions to these problems. We can make the certification a necessity or prerequisite for election for Fellowship

for men who are practicing Internal Medicine, and put up some other qualifications for those who are practicing affiliated specialties. Many of these affiliated specialties have Boards of their own, and we could equally well make it necessary for candidates from those specialties to present certification by their Boards before being elected by the College, so that we do not implicate or do not necessarily commit the College not to admit men in these other specialties, when we demand that those who are internists be certified. I feel certain that if we do not require our Fellows at least to be certified, before any great lapse of time, we would be withdrawing support from the American Board of Internal Medicine, an organization that we have sponsored."

Dr. O. H. Perry Pepper recommended that there should be published in the "Annals of Internal Medicine" some explanatory statement concerning the action taken by the Board of Regents.

There followed discussion among the Regents generally concerning an official statement to the members at the Annual Business Meeting.

The following resolution was also regularly adopted:

RESOLVED, that a Committee of three, consisting of the President, Dr. Walter L. Bierring, Chairman of the American Board of Internal Medicine, and Dr. Maurice C. Pincoffs, Editor of the ANNALS, shall be empowered to draw up an explanatory statement of the action of the Board of Regents for presentation to the members at the Annual Business Meeting.

Dr. O. H. Perry Pepper, Chairman of the House Committee of the College, reported verbally that minor alterations and final furnishing had been completed since the last meeting of the Board of Regents, and that the balance from the appropriation made at the December meeting amounted to $6.17. He said the Committee felt that the building is completed, that it is completely furnished, and that the Committee might well be discharged, the continued care of the building being left in the hands of the Treasurer and the Executive Secretary.

The Executive Secretary, Mr. Loveland, said that he felt the Committee might very well be continued, for it would be helpful to have an official Committee with whom to consult.

On motion, seconded and regularly carried, it was

RESOLVED, that the House Committee be tendered the thanks of the Board of Regents for their work, and that the Committee be continued.

President Bradley then asked Dr. Stengel if there were any additional reports to be presented by the Committee on Constitution and By-Laws.

Dr. Stengel stated that the only matter not officially acted upon was the proposed amendment providing for alternate Governors.

After general discussion, the following resolution was moved, seconded and regularly carried:

RESOLVED, that the following paragraph be added at the end of Article IV, Section 1, of the By-Laws, and that notice of the proposed addition to the By-Laws be published in the ANNALS OF INTERNAL MEDICINE at least one month in advance of the next Annual Business Meeting in 1938:

> "Any member of the Board of Governors unable to attend the Annual Session shall appoint as his alternate, with all the privileges of a Governor, a Master or Fellow of his district who will be in attendance at that Session. Upon presentation to the Chairman of the Board of Governors of a certificate of appointment, the alternate shall be recognized and act in the full capacity of Governor for the Session to which he has been appointed. The same alternate shall not be appointed for more than two consecutive years."

President Bradley stated that a number of members had suggested the propriety of having a history of the College written to date, while there are still members thoroughly conversant with all the past details since organization. Dr. Bradley thereupon appointed Dr. William Gerry Morgan to write such a history at his leisure.

On motion by Dr. James Alex. Miller, seconded by Dr. Pepper, and regularly carried, it was

RESOLVED, that the Committee on Nominations take under consideration the nomination of a Governor for the State of South Dakota, since that State now qualifies to have its own Governor.

Dr. Walter L. Bierring, Chairman of the American Board of Internal Medicine, reminded the Board of Regents that each one is an Adviser to his Board. He reported that the Board had in its files 1,030 applications for certification without examination. They had been arranged by states and cities, and the Board desires as much advice from the Regents as possible in the valuation and determination of the eligibility of these applicants. Dr. Bierring also referred to refunding to the American College of Physicians, in partial payments in annual allotments, the loan that had been made to the American Board of Internal Medicine.

Dr. Pepper suggested no action be taken until the American Board of Internal Medicine had further opportunity of reviewing their finances and determining upon a definite refunding plan.

On motion by Dr. Pepper, seconded and regularly carried, it was

RESOLVED, that the sum of $100.00 be appropriated for the uses of the College Historian, should he find need of extra clerical assistance, or in any other matters connected with preparing the history of the College.

Adjournment.

Attest: E. R. LOVELAND,
Secretary

MINUTES OF THE BOARD OF REGENTS

ST. LOUIS, MO.

April 20, 1937

The second meeting of the Board of Regents, during the Twenty-first Annual Session, was held at the Jefferson Hotel, St. Louis, April 20, 1937, with President Ernest B. Bradley presiding and the Executive Secretary acting as secretary of the meeting. On the calling of the roll, the following were recorded as present:

Ernest B. Bradley, *President*,
James H. Means, *President-Elect*,
O. H. Perry Pepper, *First Vice-President*,
Walter L. Bierring, *Third Vice-President*,
William Gerry Morgan, *Secretary-General*,
William D. Stroud, *Treasurer*,
William J. Kerr,
Roger I. Lee,
Sydney R. Miller,
George Morris Piersol,
G. Gill Richards,
Robert A. Cooke,
James B. Herrick,
Hugh J. Morgan,
James E. Paullin,
Egerton L. Crispin,
James Alex. Miller,
Francis M. Pottenger,
Charles H. Cocke,
Maurice C. Pincoffs.

Upon motion, seconded and regularly carried, the reading of the Minutes of the previous meeting was dispensed with.

Chairman Bradley called for the presentation of additional resolutions.

Dr. William Gerry Morgan, as Secretary-General, presented the following resolution on the death of Dr. Henry F. Stoll, as prepared by Dr. George Blumer, Governor for Connecticut:

HENRY FARNUM STOLL

"Whereas: The Almighty, in his inscrutable wisdom, has seen fit to remove from our midst our friend and colleague, Henry Farnum Stoll, and

"Whereas: In his unstinted devotion to duty, his lively appreciation of the importance of the public as well as the private aspects of medical practice, his constant efforts to extend the limits of knowledge in his field, and his vital interest in the welfare of his patients, he exemplified the best traditions of the medical profession, therefore,

"BE IT RESOLVED, that we place upon our Minutes a record of our sorrow at his passing and our appreciation of his many admirable qualities, and that we extend to his family our heartfelt sympathy.

—GEORGE BLUMER, M.D., F.A.C.P."

On motion, seconded and regularly carried, the above resolution was adopted.

Dr. Morgan then presented the following resolution, prepared by Dr. David P. Barr, on the death of Dr. W. McKim Marriott:

WILLIAM MCKIM MARRIOTT

"William McKim Marriott, Fellow and former Regent of the American College of Physicians, died on November 11, 1936. He was Professor of Pediatrics and for thirteen years was Dean of the School of Medicine at Washington University. As teacher and investigator, he achieved an international reputation. As a medical administrator, he saw with clarity the great problems of medical education in a rapidly changing practice. Although possessed of a fine critical faculty, he was generous and tolerant of the weaknesses and faults of others. To a remarkable degree, he was able to see the point of view of his colleagues, to reconcile conflicting opinions, to clarify issues and to accomplish joint action. Above all, he was imbued with a spirit of optimism which enabled him to ride over difficulties, to proceed after defeat and to pursue under most adverse circumstances the ideals to which he was devoted.

"Dr. Marriott's training had not been that of an administrator. He had prepared himself as a chemist, a pediatrician and a teacher. It was in these directions that he had progressed during his youth. With his numerous executive duties, with the never-ending exactions of the Dean's Office, he was able to continue the work for which he was especially qualified. It was during the period of his Deanship that his semi-annual course in pediatrics became one of the most important single factors in the postgraduate training of specialists in diseases of children. He served on the editorial board of the American Journal of Diseases of Children. He prepared and published lectures on 'Recent Advances in Chemistry in Relation to Medical Practice.' He published his classical monograph on 'Infant Nutrition.' On the busiest days he was able to make his rounds in the hospital, to supervise the innumerable activities of one of the most productive departments of pediatrics in the world. At one time he was an officer in the Southern Medical Association. He served effectively on the Council of Pharmacy and Chemistry of the American Medical Association. He was active in the formation of the Council on Foods. In the midst of all this activity, it was remarkable that he was never too busy to be available to the younger men of his staff, and was never too pre-occupied to offer them inspiration, guidance and help from his great experience. From among his pupils, universities have chosen men to fill some of the most important positions in the field of pediatrics.

"Dr. Marriott possessed one of the great medical minds of our generation. In the

breadth of his vision he had few equals. His profundity in diverse fields is attested by his achievements.

"The American College of Physicians was fortunate to have him among those who have made it one of the great medical organizations. It grieves with others in the loss of one of the great leaders in medicine and in the world of science.

—DAVID P. BARR, M.D., F.A.C.P."

On motion, seconded and regularly carried, the above resolution was adopted.

Dr. James E. Paullin, Chairman of the Committee on Public Relations, presented the following report and recommendations:

(1) That the following resignations be accepted:

Dr. Daniel F. Milam (Fellow), Hastings-on-Hudson, N. Y.
Dr. Bernard A. Manace (Associate), Toronto, Ont.
Dr. Vincent D. King (Associate), Memphis, Tenn.
Dr. Edward L. Voke (Associate), Akron, Ohio

Upon motion by Dr. William Gerry Morgan, duly seconded and carried, it was

RESOLVED, that the resignations of Doctors Milam, Manace, King and Voke be accepted.

(2) The Committee recommended that the resignation of Dr. Frederick H. Lamb (Associate), Davenport, Iowa, be held in abeyance, pending further correspondence with Dr. Walter L. Bierring, in view of the fact that the Governor for Iowa had not furnished sufficient data to enable the Committee to make a recommendation.

Upon motion by Dr. William Gerry Morgan, duly seconded and carried, it was

RESOLVED, that the resignation of Dr. Frederick H. Lamb (Associate), Davenport, Iowa, be held in abeyance, pending further correspondence with Dr. Walter L. Bierring.

(3) The Committee recommended that the dues of Major F. R. Borden (Fellow), M. C., U. S. Army, retired, be remitted because of physical disability.

On motion by Dr. James Alex. Miller, duly seconded and regularly carried, it was

RESOLVED, that the dues of Major F. R. Borden, M. C., U. S. Army, be remitted because of physical disability.

(4) The Committee recommended that the letter of Dr. E. M. Stevenson, of Bloomington, Ill., be returned to the Executive Secretary without comment.

Upon motion, seconded and regularly carried, the entire report of the Committee on Public Relations was adopted.

Dr. James Alex. Miller reported, as Chairman of the Committee on Future Policy for the Development of Internal Medicine, as follows:

"A meeting of the Committee on Future Policy for the Development of Internal Medicine was held on April 19, 1937. There were present Dr. James Alex. Miller, Chairman; Dr. F. M. Pottenger; Dr. Maurice C. Pincoffs; and Dr. Roger I. Lee.

"The various proposals concerning the future policy of the College were considered, and, in general, it was the concensus of opinion that the chief emphasis in future policy should be upon efforts to improve postgraduate education in Internal Medicine in this country, and, particularly, for Fellows and Associates of the College.

"1. The suggestion that the College set up a revolving loan fund to aid candidates for certification by the American Board of Internal Medicine, so that candidates might be enabled to undertake studies which would fit them to meet the requirements of these examinations was recommended as worthy of approval by the Regents if and when the financial resources permit.

"2. The recommendation that the College establish lectureships to be given by outstanding internists, both from foreign countries and the United States, was considered, but the Committee does not deem it wise at the present time at least to recommend this as a policy for the College.

"3. Dr. Herman Mosenthal presented a proposition for the establishment of regular short courses for postgraduate students in Internal Medicine in certain selected medical centers. It was Dr. Mosenthal's suggestion that the College consider the appropriation of a sum of money to provide for an executive secretary to organize and administer such courses. This proposition was not approved by the Committee.

"4. It was brought to the attention of the Committee that a tentative movement is on foot to provide a survey of all postgraduate facilities in the United States and that it had been intimated that funds for conducting such a survey might be available, if the need for it was indicated on the part of representative medical organizations. The Committee voted to recommend to the Regents that they approve a plan for such a national survey of postgraduate facilities as far as it relates to Internal Medicine, provided that the survey was planned and conducted under suitable auspices and provided that as a part of the survey some plan for a continuing organization which would afford opportunities for information and guidance for prospective postgraduate students was proposed.

"5. The Committee thoroughly discussed the desirability of the College doing something of a specific nature to provide postgraduate courses for its Fellows and Associates. As a result of this discussion, it was specifically recommended that the Board of Regents consider the feasibility of providing special short courses in various branches of Internal Medicine to be held at about the time of each Annual Session. These courses to be organized both in the city where the Session is held and in conveniently located near-by medical centers. It was suggested that such courses might be of two weeks' duration and be conducted either immediately before or immediately after the week of the general Session. It was also recommended that the Regents consider giving some financial assistance to the organization of such courses, so that any fees that were charged could be kept very low. It was specifically suggested that an assistant to Mr. Loveland might be provided to take charge of this work.

"6. The Committee also discussed the policy the College should have in the future toward its commercial exhibits. It is the opinion of the Committee that the character of the commercial exhibits should be kept of a very high order, and that the College should bear in mind that in the future it should not be wholly dependent upon the income from the commercial exhibits so as to in any way influence the character of the exhibits. Toward this end, it was suggested that the Board of Regents might appoint a subcommittee to make a special study of this question.

"7. The general question of the future policy of the College, as it relates to membership in the various allied specialties and, particularly, as it relates to the policy of the College toward the American Board of Internal Medicine was discussed. It was the sense of the Committee that the action in delaying the proposed changes in the Constitution and By-Laws concerning these questions is wise, but the Committee wishes to emphasize to the Board of Regents its strong feeling that the policy of the College should gradually extend toward a raising of standards which eventually might reach the standards set in the proposed amendments, to the end that the standards of practice in Internal Medicine in general may be raised and that Fellowship in the College may be increasingly considered as an honor.

"In connection with the problem of the allied specialties, it was the feeling of this Committee that the retention of a certain number of Fellows representing these specialties would be desirable, but that in the future any applications for Fellowship in this class should be scrutinized with especial care and should ultimately probably require the certification of each candidate by his own special National Board or, lacking that, its equivalent in professional or scientific achievement."

Discussion of the Report:

Item four: Dr. Miller explained that this proposal is simply a matter as to whether the Board of Regents desires to place on its Minutes the approval of the recommendation of

the Committee that there should be considered, under proper safeguards, a survey of postgraduate facilities in Internal Medicine. Dr. Miller said his Committee was unanimously in favor of it, and offered a resolution that the recommendation be adopted. The motion was seconded by Dr. Kerr.

In the discussion of the motion, it was again pointed out that the recommendation could not be made more specific at the present time, because the plan will come back again when it is consummated; but, in order to get the survey started, a few medical organizations would have to say that they think such a survey, properly conducted, would be desirable.

Chairman Bradley inquired about the source of funds for such a survey. Dr. Miller replied that funds might be provided from two of the large foundations; but these foundations would wish to know first whether the American College of Physicians and the New York Academy of Medicine believe such a survey would be useful and desirable.

Dr. Pincoffs suggested that this motion should be sent to the Council on Education of the American Medical Association, so that the College would be dealing at once with them, and with any one else who might be interested in such a survey, showing that the resolution by the College does not designate any foundation, but merely indicates the desirability of such a survey, under proper auspices.

The motion was then put to vote and regularly carried:

RESOLVED, that the American College of Physicians approve in principle that a survey of all postgraduate facilities of the United States would be desirable, so far as it relates to Internal Medicine, providing that the survey be planned and conducted under suitable auspices, and providing that as a part of the survey, some plan be proposed for a continuing organization, which will afford opportunities for information and guidance for prospective postgraduate students.

Discussing recommendation "five" of the Committee, Dr. Miller said:

"This is a very far reaching suggestion, looking toward an effort to do something specifically for our College members, and to do it in a way which they would feel in a large part is a contribution open to them because of their Associateship or Fellowship in the College, and an opportunity to extend the College's postgraduate activities. These courses would be open only to Associates and Fellows of the College. It would be determined in advance what courses are available in the city, or near-by cities, where our courses would be conducted. The members of the College would have to be circularized through the 'Annals,' and in every other way. It might add to the prestige of the College, and we hope it would add to the services extended to our membership. We were hoping that the fee charged might be a nominal one, perhaps $10.00. The proposal involves a consideration of honoraria to those giving the courses, or, perhaps, from the beginning the plan might be tried on an honoraria basis. The plan might involve the appointment of an assistant to the Executive Secretary who would be competent to do some medical work in the College. The courses would naturally be organized by a local group, but could be organized in any manner desired, with the courses being offered not only by Fellows of the College, but by others who might be selected.

"The recommendation before the Regents, first, requires the approval of the principle, and, secondly, requires consideration of ways and means of carrying it out and expenditures therewith involved. If approved, the proposal probably involves the appointment of a special committee. It seems to me that today we might go so far as to approve the principle of giving such services to our Fellows and Associates, by these short courses at about the time of the Annual Sessions. If this proposal should be undertaken next year, and the Annual Meeting should be held in New York City, courses could readily be organized, using the facilities of New York, of Philadelphia, of Boston, and of New Haven, at least for such clinics. There should be no great difficulty in organizing two-week courses in all the various branches of Internal Medicine. I move the approval of the Board of Regents of the project as a desirable activity of the

College, and the appointment of a special sub-committee to be concerned solely with the project."

The motion was seconded by Dr. William Gerry Morgan.

In the discussion, Dr. Miller pointed out that if expenditures should be involved, the Executive Committee of the Board of Regents has power, in the interim, to act on all necessary expenditures.

Dr. James E. Paullin expressed his hearty approval of the proposal, but asked that the Committee might even broaden its scope. There have been springing up all over the country various postgraduate courses. The College might be able to serve a very useful purpose, and instead of limiting its postgraduate activities to just before the Annual Meeting, it could sponsor, conduct and supervise postgraduate courses in the various districts of the country, bringing the courses near at hand to the members, and not requiring so much of their time for the Annual Meetings, often conducted at a long distance removed from their homes.

Dr. Miller pointed out that in his opinion, for the first year or two, the College might better confine its activities to one set of courses, perfect its method of organization, get more experience, and then probably expand the principles, if it works out successfully. Furthermore, by that time, the survey of postgraduate facilities might be completed, and the Committee probably could report back on further procedure.

The motion was then put to a vote, and unanimously carried:

RESOLVED, that the Board of Regents approve of the feasibility of providing special postgraduate courses in various branches of Internal Medicine to be held at about the time of each Annual Session, these courses to be organized both in the city where the Session is held and in conveniently located, near-by medical centers; further, that the Board of Regents approve the appointment of a special sub-committee to be concerned solely with this project.

In further commenting upon the action taken, Dr. Pincoffs suggested that the members of the Board and the committee, when appointed, consider the project carefully, so that they will be ready for definite action at the 1937 autumn meeting of the Board of Regents.

Dr. James Alex. Miller pointed out that the committee should bear in mind that there is a definite implication that the fees charged to our members should be kept as low as possible.

Dr. Miller further said that the medical assistant might find many avenues of service to the College which might materially strengthen the Organization.

In discussing item "six" on the report of the Committee, concerned with the matter of commercial exhibits and advertising, Dr. Miller emphasized the need for a complete study of both exhibits and advertising, with a view to keeping both on the highest possible plane. In regard to exhibits, the suggestion was made that perhaps they could be somewhat more restricted in their extent, with the elimination of any exhibit that is not specifically relevant to the practice of Internal Medicine, or one of its affiliated specialties.

Upon motion by Dr. James Alex. Miller, seconded by Dr. William Gerry Morgan, and regularly carried, it was

RESOLVED, that the Committee on Advertising and Commercial Exhibits, as presently constituted, be terminated, and that a new Committee be appointed by the incoming President; the duties of the Committee to make a survey and to formulate future policies for the acceptance of advertisements in the "Annals of Internal Medicine" and the acceptance of exhibits for our Annual Sessions.

No action was required on item "seven" of the Committee's report. However, item "one" on the report, not previously discussed, was again reviewed, namely, the setting up of a revolving loan fund to aid candidates seeking certification by the American Board of Internal Medicine, enabling them to undertake studies which would fit them to meet the requirements of these examinations.

Dr. Maurice C. Pincoffs, speaking on the matter, said: "It occurs to me that the College is playing a considerable part in making it harder for men to enter Internal Medicine, and

that we stand in not a little danger of having our internists selected by their financial capacity, rather than by their character and by their brains. The College might well do something to help some of these younger men who may be crowded out of the career of Internal Medicine, though they are well fitted for it in every other way than finances. There are throughout the country a great number of revolving loan funds in connection with undergraduate and, to some extent, graduate work. There is in New York a foundation which itself operates such a fund, and which has made a study of the broader question of revolving loan funds. While we may not be able to take action today, it seems to me a project well worthy of studying, and a committee might be appointed by the President to obtain the assistance of that foundation, which was offered gratis and very willingly, in working out a definite and specific plan on the basis of its experience with revolving loan funds in general among students and graduates, the committee to submit their findings at the autumn meeting of the Board of Regents, so that the matter may be considered in terms of experience, in dollars and cents, in relation to our finances."

On motion by Dr. Pincoffs, seconded by Dr. Kerr, it was

RESOLVED, that the Board of Regents shall appoint a special committee for the purpose of studying the question of the operation of revolving loan funds for medical graduates preparing for certification.

Speaking to the motion, Dr. Kerr said in part: "One of the problems confronting us is that a number of younger men who are encouraged, and, perhaps, expected, to spend a year or more in one of the basic sciences, or fundamental branches of medicine, after their medical school years, may not be able to do so. It, therefore, seems to me if we could provide the means for this in some measure through a loan fund, we would reap the benefits. I was very much impressed by the recommendations of the Committee on Future Policy for the Development of Internal Medicine in other directions, looking toward postgraduate education. I think they are all in the right direction, and it seems to me that the College is now beginning to have some real objectives, objectives that our Governors and Fellows have been looking for us to establish."

The motion was put to a vote and unanimously adopted.

The appointment of the Committee was left to the incoming President.

On motion by Dr. Paullin, duly seconded and carried, it was

RESOLVED, that the Board of Regents adopt the report, as a whole, of the Committee on Future Policy for the Development of Internal Medicine.

Dr. Pincoffs had no specific report as Editor of the ANNALS OF INTERNAL MEDICINE, saying that his report will be covered by the report of the Committee on the ANNALS, which will be given by the Chairman, Dr. Means.

Dr. James H. Means, Chairman of the Committee on the ANNALS, reported that a meeting had been held with all members of the Committee present, and with the Editor, Dr. Stroud and Dr. Pepper present by invitation. The affairs of the ANNALS had been discussed with the Editor, and no specific recommendations were presented. The chief item of consideration had been that of festschrifts, particularly a festschrift for Dr. Joseph H. Pratt, of Boston. The Editor's policy in regard to the handling of festschrifts was considered further by the Committee.

At this point, Dr. Pincoffs explained that in selected cases where an anniversary volume is to be published in honor of some outstanding medical authority, certain of the articles might be accepted for publication in the ANNALS OF INTERNAL MEDICINE, so that they may have a permanent place in medical literature, the right to be reserved to publish only such of those articles as the Editor might feel meet the standards of the ANNALS. They will be published with a modest heading, explaining that they are to form a part of an anniversary volume. The College, or the ANNALS, will take no part in organizing or sponsoring a festschrift to any one, merely adopting the policy of publishing in the ANNALS, under proper heading, suitable material from such festschrift. The ANNALS may gain considerable valuable material in this manner. The first articles from the festschrift of Dr. Joseph H. Pratt,

of Boston, marking his sixty-fifth birthday, will appear in the May, 1937, issue of the ANNALS, and continue through December. The committee in charge of the festschrift has made its own arrangements with our publishers, so that the type from these articles in the ANNALS can later be used in publishing its volume, to which will probably be added such other festschrift articles as have not been accepted for the ANNALS. Dr. Pincoffs said that it is his belief that this is the first time any medical journal has undertaken this matter, and expressed the hope that it is going to have some merit in adding to the value of festschrifts in the future. So often they are a total loss to medical literature.

Dr. Walter L. Bierring reported that the American Board of Internal Medicine had discussed the method of refunding its financial obligation to the College, and that it had taken action authorizing the refunding to the College at this time $5,000.00 of its loan, and a check for said amount was delivered to the College.

Dr. William D. Stroud, Treasurer, presented the following report:

"To the Board of Regents:

"As of March 31, 1937, the College has invested securities of a book value amounting to $101,857.00; of this amount, $58,853.00 is in the Endowment Fund and $43,004.00 is in the General Fund; $82,250.00, or 80.75% of the above amount is invested in bonds; $4,741.00, or 4.65% is invested in preferred stocks, and $14,866.00, or 14.60% is invested in common stocks. In addition, the college has in bank balances $47,470.00, making a total of $149,328.00 as compared with a total of $157,329.00 approximately one year ago at the time of the last yearly meeting.

Respectfully submitted,

(Signed) WILLIAM D. STROUD, *Treasurer*"

He pointed out that in spite of having purchased the new College Headquarters and having paid for the improvements and furnishings, the invested capital of the College was only $8,000.00 less than a year previous.

Upon motion by Dr. James Alex. Miller, seconded by Dr. William Gerry Morgan, it was RESOLVED, that the report of the Treasurer be accepted and placed on file.

Dr. James Alex. Miller, as Chairman of the Committee on Finance, presented the following report:

"A meeting of the Finance Committee was held on April 19, 1937. There were present Dr. James Alex. Miller in the Chair, Dr. Roger I. Lee and Dr. William D. Stroud.

"The financial statements were submitted by the Treasurer and by the Executive Secretary, and also an analysis of the present investment list by the Investment Counsel. Upon recommendation of the Treasurer and of the Executive Secretary, it was decided that $15,000.00 might be safely withdrawn from the available cash funds in the General Fund for investment. It was voted to approve the investment of this amount for the General Fund account in securities later to be approved upon the recommendation of the Investment Counsel. Upon recommendation of the Investment Counsel, the sale of $5,000.00 of Chesapeake and Ohio, 3½s, due 5–1–96, was authorized. This is for the Endowment Fund account. Also, upon the recommendation of the Investment Counsel, it was authorized to sell the following:

50 Shares General Motors Corporation, common
45 Shares Mid-Continent Petroleum Corporation
70 Shares National Breweries, Ltd., common

These three transactions are for the General Fund account.

"Also, it was voted to authorize to buy for the Endowment Fund account $5,000.00 of Northern States Power Company, First Refunding 3½s, due 2–1–67. It was also voted to buy for the General Fund account, 50 Shares of Chase National Bank of New

York, common stock, and 30 Shares of Pacific Gas and Electric Corporation, 6%, cumulative preferred.

"The recommendation of the Investment Counsel to invest the remaining $3,300.00 realized from the above sales for the General Fund account in U. S. Treasury, 1½s, was not approved, but it was voted to invest this amount, together with the $20,000.00 above approved for investment for the General Fund account."

In commenting upon the report, Dr. Miller stated that his Committee finds the financial situation of the College most satisfactory. He expressed full satisfaction and appreciation of the value of the services of our Investment Counsel. This Counsel has been of constant aid to the Committee, and in their recent survey commended very highly the character of the College investments.

Upon motion by Dr. James Alex. Miller, seconded by Dr. William Gerry Morgan, it was voted that the report of the Finance Committee be accepted and adopted.

At this point in the program, the Washington, D. C., delegation was admitted, in order that it might present its invitation to the College to hold its 1939 Annual Session in Washington.

An invitation to meet in Washington, D. C., in 1939 was extended by Dr. William Gerry Morgan, Secretary-General, by Dr. Wallace M. Yater, Governor for the District of Columbia, by Dr. Thomas Parran, Surgeon General of the U. S. Public Health Service, by Admiral Perceval S. Rossiter, Surgeon General of the U. S. Navy and by Dr. Robert U. Patterson, former Surgeon General of the U. S. Army.

Dr. Charles H. Cocke, Chairman of the Board of Governors: "The Board of Governors, being deeply sensible of, and deeply grateful for the hospitality of the Regents during recent years, instructed me to invite you to be their guest at the next Annual Meeting, on the Sunday evening preceding the opening of the Session."

Dr. Cocke further reported that there had been the largest attendance by members of the Board of Governors in the history of the College.

President Bradley expressed the thanks of the Regents for the invitation from the Governors, and accepted the invitation on behalf of the Regents.

President Bradley then reported that there had been a special committee, consisting of the President, President-Elect and the First Vice President, appointed during December, 1936, to confer with a committee from the American College of Surgeons on general subjects. Such a meeting was held at St. Louis with Dr. George Crile and Dr. Irvin Abell, representing the American College of Surgeons; Dr. Crile being Chairman of their Board of Regents, and Dr. Abell being the Secretary. Out of the meeting grew no definite recommendations to be made to the Board of Regents of the American College of Physicians. Dr. Bradley, however, recommended that a like committee be appointed during the coming year to continue these conferences.

Dr. Bradley thereupon called upon Dr. Maurice C. Pincoffs to read the statement concerning the withdrawal of the amendments to the Constitution and By-Laws, as authorized at the preceding meeting of the Board of Regents, which Dr. Pincoffs presented as follows:

"It is the feeling of the Regents that the standards for admission to the College should be progressively raised. A change in the By-Laws, making certification by the American Board of Internal Medicine a prerequisite to Associateship, was considered in recent months by the Regents. It was felt, however, that this would at this time constitute too radical an increase in the requirements, and so this proposed amendment has been withdrawn. After further consideration, other proposals for increasing the standards will be submitted to the College.

"Another amendment discontinuing the admission to the College of physicians working in fields allied to Internal Medicine has likewise been withdrawn by the Regents. It is the present feeling of the Regents that the admission of a certain number of Fellows representing these specialties would be desirable. Any application for Fellowship

in this class should be scrutinized with especial care, and should ultimately probably require the certification of each candidate by his own special certifying Board, or, lacking that, its equivalent in professional or scientific achievement."

Upon motion by Dr. James Alex. Miller, seconded by Dr. Walter L. Bierring, and regularly carried, it was

RESOLVED, that the Board of Regents approve of the above statement.

Dr. Charles H. Cocke, as Chairman of the Board of Governors, again inquired about the matter of alternate Governors. He reported that alternate Governors had been seated at the present meetings by agreement within the Board of Governors.

President Bradley said that he felt there would be no objection to this action until the particular amendment to the By-Laws has been officially adopted.

The Executive Secretary then presented a report on the Associates who were elected at the 1932 Annual Session. The following analysis was presented:

Qualified for Fellowship	70
Deceased	3
Resigned	2
Failed to take up election	1
Dropped	9
Total candidates elected '32 Session	85

Nine Associates elected at the 1932 Session were automatically dropped for failure to present the requisite credentials for Fellowship within the five-year maximum period, as provided by the By-Laws.

Six Fellows and 5 Associates were by resolution discontinued on the Roster of the College because of delinquency of more than two years' standing.

The Executive Secretary then presented to members of the Board of Regents copies of the pamphlet in which all gifts to the College Library have been recorded, the pamphlet being an index to the College Library of publications by members. A sufficient quantity of these indices have been printed, and were being given to all members interested at this Session.

Mr. Loveland then called to the attention of the Board of Regents that a new Directory of the College would be published during the coming summer. He asked for directions in two respects: (1) whether it is the wish of the Board of Regents that the Directory continue to carry the names of Associates, as well as Masters and Fellows; (2) he suggested the appointment of a consulting committee to consider what specialty listings would be approved for record in the Directory.

In the discussion that ensued, it was the consensus of opinion that the Associates should continue to be listed in the Directory, and that a plan should be worked out by which those consulting the Directory would not likely confuse Associates with Fellows.

On motion by Dr. James Alex. Miller, seconded by Dr. Walter L. Bierring, and regularly carried, it was

RESOLVED, that there shall be appointed a committee of three to act in a consulting capacity in regard to the publication of the new Directory, this committee being delegated power to decide on the manner of listing Associates, and the list of sub-specialties to be recognized.

Adjournment.

Attest: E. R. LOVELAND,
Executive Secretary

MINUTES OF THE BOARD OF REGENTS

St. Louis, Mo.

April 23, 1937

The final meeting of the Board of Regents, during the Twenty-first Annual Session, was held at the Jefferson Hotel, St. Louis, April 23, 1937, with President James H. Means presiding, Mr. E. R. Loveland acting as secretary, and with the following Regents present:

James H. Means, *President*,
William J. Kerr, *President-Elect*,
David P. Barr, *First Vice-President*,
G. Gill Richards, *Second Vice-President*,
William Gerry Morgan, *Third Vice-President*,
William D. Stroud, *Treasurer*,
Ernest B. Bradley,
O. H. Perry Pepper,
Walter L. Bierring,
Hugh J. Morgan,
James E. Paullin,
Egerton L. Crispin,
James Alex. Miller,
Francis M. Pottenger,
Charles H. Cocke,
Maurice C. Pincoffs.

Upon motion duly seconded and carried, it was Resolved to dispense with the reading of the Minutes of the preceding meeting of the Board of Regents.

The Chairman recognized Dr. John H. Musser, of New Orleans, who presented an urgent invitation for the College to hold its 1939 Annual Session in New Orleans.

The Chairman also recognized Dr. William J. Kerr, of San Francisco, who presented a like invitation for the College to hold its 1939 Annual Session in San Francisco.

Dr. Bradley reported that some of the Cincinnati Fellows of the College had expressed to him the desire to extend an invitation to the College to meet in Cincinnati. Dr. Bradley stated that he was herewith presenting the invitation from Cincinnati, to consider that City some year in the future. He reviewed the general and clinical facilities of Cincinnati for holding the meeting.

At this point, the secretary, Mr. Loveland, was asked to read the invitation of the City of Cleveland, in the absence of Dr. Willard C. Stoner, who had been unable to remain for this meeting.

Mr. Loveland presented the invitation prepared by Dr. Stoner for the College to select Cleveland for its 1939 Annual Session. He also reported that he had before him telegrams from the Mayor of Cleveland, from the Convention Bureau, from the Dean of Western Reserve University School of Medicine and from the Academy of Medicine of Cleveland, all urging the acceptance of Cleveland for the 1939 Session.

Mr. Loveland also reported that there was still outstanding an invitation from Memphis for one of the Annual Sessions of the College.

The Chairman, Dr. Means, then recognized Dr. James Alex. Miller.

Dr. James Alex. Miller: "I may say that since the last meeting of the Board of Regents, when New York's invitation was first suggested, or offered, we have had an expression of medical interest in the College on behalf of very outstanding members of the Medical Profession, and from inquiries which some of us have made, there is no doubt whatever that if we decide to come to New York next year, you are going to have 100 per cent cooperation from all the large medical centers.

"Also, from preliminary surveys of the opportunities that will be offered from the standpoint of hotel accommodations, accommodations for the clinical staff, for the round tables, for the exhibits, and all of that part which has to do with the executive side of the Session, it seems as though if we do decide to come to New York next year, and we decide fairly soon, we will be able to get what we consider ideal accommodations.

"So that, on behalf of the Officers of the College, resident in New York, and also on behalf of a large number of others, including the Mayor and others who are interested in New York as a convention center, whose communications I will not take the trouble to read to you, we can offer you a very hearty invitation, and I think we can promise to put on a very good meeting for the College at that time."

At this point, the Chairman recognized Dr. M. A. Shillington, of St. Paul, who presented an invitation to the College to select St. Paul for its 1939 Annual Session. Dr. Shillington discussed in detail the facilities of St. Paul and the advantages of holding an Annual Session of the College in that City.

Dr. Charles H. Cocke, Chairman of the Board of Governors, was called upon for a report of that Board. He stated that at the second meeting of his Board, thirty-nine members had been present, and that they had received the report from the Board of Regents with interest and earnest consideration. The Board of Governors wished to recommend to the Consulting Committee on the Directory that the Associates be listed in the Directory, but in the geographical index be designated as "Associates" and listed immediately under the same States and cities as the Fellows.

The Board of Governors had voted unanimously to recommend to the Committee on Postgraduate Study, through the Board of Regents, that the courses be developed as soon as practicable, and that they should be of a minimum of not less than two, or of a maximum of not more than four weeks' duration.

The Board of Governors also had voted unanimously to recommend to the Board of Regents that the "allied specialties" be retained in the Constitution.

On motion duly seconded and regularly carried, it was

RESOLVED, that the report from the Board of Governors be received and recorded.

At this point, the order of business called for the election of the Treasurer and Secretary-General for 1937–38.

On motion by Dr. Paullin, seconded by Dr. Richards, and unanimously carried, Dr. William D. Stroud was nominated for reëlection as Treasurer. As there were no other nominations, Dr. Stroud was declared elected.

Dr. William Gerry Morgan: "Mr. President, I wish to put in a nomination, but before doing so, I want to take this opportunity to express my profound and heartfelt appreciation for the honor extended to me and the courtesies which I have received during my incumbency. My experience during these four years has shown me that it would be very much to the advantage of the College to have a Secretary-General in Philadelphia. There is such a constant exchange of material and matters between the Executive Secretary and the Secretary-General that it would facilitate the carrying on of these business affairs, and it would be a saving to the College from the point of postage and otherwise. Therefore, I take the very greatest pleasure in nominating Dr. George Morris Piersol as Secretary-General."

The nomination of Dr. Piersol was seconded by Dr. Bradley. There were no other nominations and Dr. George Morris Piersol was unanimously elected Secretary-General.

The Chairman recognized Dr. S. Marx White, who entered at this time to second the invitation for the College to select St. Paul for its 1939 Session.

President Means then called for the election of an Executive Committee for 1937–38, reading the provisions in the By-Laws governing the same. The President, the President-elect, the Secretary-General and the Treasurer are members of the Executive Committee ex officio. The five additional members formally elected were as follows:

Walter L. Bierring, Des Moines
Roger I. Lee, Boston
James Alex. Miller, New York
Hugh J. Morgan, Nashville
Maurice C. Pincoffs, Baltimore

President Means then proceeded to the matter of the appointment of committees, reading the personnel of standing committees, the regulations governing same and the names of those whose terms have expired.

The following appointments were made:

COMMITTEE ON ADVERTISEMENTS AND COMMERCIAL EXHIBITS

George Morris Piersol, Chairman, Philadelphia
William D. Stroud, Philadelphia
William Gerry Morgan, Washington

COMMITTEE ON THE ANNALS OF INTERNAL MEDICINE

Walter W. Palmer, New York (term expiring 1940)—taking the place of Dr. Egerton L. Crispin, whose term expired. Dr. Means relinquished the Chairmanship and appointed Dr. David P. Barr, already a member of the Committee, to act as Chairman.

COMMITTEE ON FELLOWSHIPS AND AWARDS

James D. Bruce and Egerton L. Crispin appointed in the place of James H. Means and William J. Kerr.

CONSULTING COMMITTEE ON ANNUAL SESSIONS

Appointments automatic—the Committee for 1937–38 shall consist of:

James H. Means, Boston, *Chairman*
James Alex. Miller, New York
David P. Barr, St. Louis
Ernest B. Bradley, Lexington

COMMITTEE ON CONSTITUTION AND BY-LAWS

Alfred Stengel (term expiring 1940), reappointed to succeed himself.

COMMITTEE ON CREDENTIALS

George Morris Piersol (term expiring 1940), reappointed to succeed himself from the Board of Regents.

Ernest B. Bradley (term expiring 1938), to fill out the unexpired term of the late Dr. Luther F. Warren.

Dr. Cocke reported that he had reappointed from the Board of Governors, Dr. William B. Breed (term expiring 1940).

COMMITTEE ON FINANCE

Roger I. Lee (term expiring 1940), reappointed to succeed himself.

COMMITTEE ON NOMINATIONS

(President Means announced that he would make his appointments to this Committee in accordance with the By-Laws, within thirty days.)

COMMITTEE ON PUBLIC RELATIONS

Walter L. Bierring (term expiring 1941), reappointed to succeed himself.

(James H. Means, as President, becomes a member of this Committee, ex officio, succeeding Ernest B. Bradley.)

AMERICAN BOARD OF INTERNAL MEDICINE

Representatives appointed by the American College of Physicians included the reappointment of Jonathan C. Meakins (term expiring 1940), and the reappointment of G. Gill Richards (term expiring 1940).

HOUSE COMMITTEE

(The House Committee, consisting of O. H. Perry Pepper, William D. Stroud and James Alex. Miller, had already been reappointed by the Board of Regents at an earlier meeting.)

COMMITTEE ON FUTURE POLICY FOR THE DEVELOPMENT OF INTERNAL MEDICINE

(The entire Committee listed below was reappointed)

James Alex. Miller, New York, *Chairman*
Walter L. Bierring, Des Moines
Roger I. Lee, Boston
Maurice C. Pincoffs, Baltimore
Francis M. Pottenger, Monrovia

COMMITTEE ON POSTGRADUATE SURVEY

William J. Kerr, San Francisco, *Chairman*
Charles H. Cocke, Asheville
Hugh J. Morgan, Nashville

COMMITTEE ON REVOLVING LOAN FUND

Maurice C. Pincoffs, Baltimore, *Chairman*
Roger I. Lee, Boston
Francis M. Pottenger, Monrovia

Upon motion by Dr. W. D. Stroud, seconded by Dr. F. M. Pottenger, and unanimously carried, it was

RESOLVED, that the 1938 Annual Session of the College be held in New York City.

Upon motion by Dr. G. Gill Richards, seconded by Dr. Walter L. Bierring, and unanimously adopted, it was

RESOLVED, that Dr. James Alex. Miller be appointed General Chairman of the 1938 Annual Session.

In responding, Dr. Miller expressed his appreciation both for the selection of New York City and for the confidence expressed in his ability by his appointment as General Chairman. He said everything possible would be done to make the meeting successful. Dr. Miller discussed the matter of the date of the meeting and asked for advice and counsel in all matters from the Board of Regents. He stated that he and the Executive Secretary had already been looking into the facilities of the various hotels in New York, and that they would proceed in accordance with instructions from the Board to designate the headquarters and to select an open date. The opinion had been expressed that a meeting early in March would not be particularly popular, because it breaks up the continuity of winter work for a good many fellows and, perhaps, breaks into the curriculum of the undergraduate teaching in the medical centers. He particularly suggested the week beginning April 3 and the week beginning May 10, as possible appropriate times for the meeting.

Dr. James Alex. Miller, Chairman of the Finance Committee, expressed the appreciation of the Board for the extraordinary services that the Executive Staff of the College performed, with the large amount of work and extra time devoted to the work by the Executive Secretary and his staff.

On motion by Dr. Richards, seconded by Dr. Crispin, and regularly carried, it was

RESOLVED, that the Finance Committee shall take under advisement increases in salary for the Executive Staff, with power to act.

Dr. Ernest B. Bradley, retiring President, at this point took the opportunity to thank the members of the Board of Regents for their coöperation with him during his term as President. He recommended that in the future the President should not have charge of the Morning Lectures and Round Tables, but rather that these should be assigned to the General Chairman, because the General Chairman in arranging his Clinics should arrange the entire morning program. He expressed the opinion that both of these additions to the program were well justified, as indicated by the large attendance daily. The Morning Lectures were attended by groups numbering from two hundred to four hundred, and the Round Tables turned out to be exceedingly popular.

Dr. James Alex. Miller pointed out that in his opinion, it is impossible to make up a program of Morning Lectures independent of the General Sessions. There must be close coöperation between the two, he said, and he recommended that possibly the President and the General Chairman might divide the responsibility jointly.

Dr. Bradley pointed out that he and the General Chairman, Dr. Barr, had consulted frequently, and had worked out all the program, more or less, together. Dr. Bradley also pointed out that those who had participated in the last two Annual Sessions are members of the Consulting Committee on Annual Sessions, and are available to help at all times the President and General Chairman.

President James H. Means forwarded the suggestion that the President take charge of the Morning Lectures, so that they may harmonize with the General Sessions, and that the Chairman take charge of the program of Round Tables.

There was general discussion among the members of the Board concerning the propriety of conducting a program of Morning Lectures, some feeling that such a program is unnecessary and that it may conflict with the attendance at the Clinics.

Dr. Bradley pointed out that the entire St. Louis program was worked out around the suggestions of the requests of the members. There are those who prefer to attend Clinics, others who prefer the practical Morning Lectures, and a great host who asked for the addition of the Round Tables. He emphasized the importance of giving the members of the College at large what they personally want on the program, rather than dictating what they should have.

Dr. Barr disclosed that he had not been in favor of the Morning Lectures, because he felt that they would greatly interfere with his program of Clinics. However, as the meeting turned out, the Morning Lectures were a great advantage in view of the fact that the meeting had been so much larger than expected, that had it not been for the Morning Lectures to take care of overflows, the Clinics would have been swamped. He expressed the opinion that the Morning Lectures might be highly appropriate in the smaller cities where clinical facilities are limited, but that the program might be abbreviated in larger cities where there are unlimited clinical facilities.

Dr. Bradley referred to an editorial written by the late Dr. Aldred Scott Warthin, some years ago, in which he recommended that at least one session be devoted to the discussion of general questions. He recommended that this might be considered by the program committee for the following year.

Dr. William J. Kerr decried the tendency of morning clinics developing into lectures, rather than into practical demonstrations, with the showing of patients. The members at large do not want just an additional set of lectures given as clinics, but they desire real clinics with the demonstration of patients and the discussion of cases. Several endorsed the opin-

ions expressed by Dr. Kerr and emphasized the importance of arranging programs of real clinics at future meetings. Some expressed the opinion that the St. Louis clinics had been an improvement in this respect over the clinic programs given in some other cities.

Dr. James Alex. Miller inquired whether those who attend the Morning Lectures are merely the indolent ones who do not get up in time to reach the clinics; and, if such were the case, whether the Morning Lectures should not be delayed until ten-thirty in the morning, and only give a course for an hour or an hour and a half.

Dr. Bradley pointed out that in his opinion men went to the Morning Lectures because they were interested in them, and not because they didn't get up in time to go to the Clinics.

Dr. Barr reported that the Clinics, especially at the Barnes Hospital, had been largely oversubscribed, and that as many as two hundred had been turned away from some Clinics because of lack of room to accommodate them. An attempt had been made to engage doormen so that those who had reserved tickets would be assured of admission.

Someone pointed out the necessity of scheduling the Round Tables at the New York Session at such time that those attending the Clinics would be able to get back to the Round Tables on time, so that those attending the Round Tables would not be disturbed by attendants coming in continuously throughout the hour.

Dr. Richards pointed out that the most distinguishing feature in the Annual Sessions of the American College of Physicians is the program of clinics. He recommended that where possible clinics should be provided for in such quantities as to accommodate every one who desires to attend.

There was some discussion about holding some of the Round Tables at the medical centers where clinics would be conducted in New York. Dr. Miller said that this very likely could be arranged at the Presbyterian Hospital, but that other centers would be sufficiently close to the headquarters to make it possible for attendants to return in time for the Round Tables. He further referred to the very excellent facilities at the Waldorf-Astoria Hotel for many Round Tables, with the additional facilities for luncheons.

Dr. Barr recommended that there be a gap of a half hour for transportation between the end of the Clinic program and the beginning of the Round Table program. This had not been so arranged at St. Louis, with the result that there had been much difficulty in the attendants getting back for the Round Tables.

Adjournment.

Attest: E. R. Loveland,
Executive Secretary